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CLINICAL NUTRITION

Edited by
NORMAN JOLLIFFE, M.D.
F. F. TISDALL, M.D. *and* PAUL R. CANNON, M.D.
For the Food and Nutrition Board
of the National Research Council

WITH 78 TABLES AND 127 ILLUSTRATIONS, 61 IN FULL COLOR

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CLINICAL NUTRITION

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Foreword

The difficulty encountered by physicians in the diagnosis of nutritional abnormalities has been a subject of concern to the Food and Nutrition Board since its establishment in 1940 by the National Research Council. The frank deficiencies have long been recognized but they occur infrequently, whereas experience with animals in the laboratory and on the farm leads to the presumption that for every case of scurvy, beriberi, or pellagra there must be many cases of less severe degrees of human malnutrition which escape detection. The diagnostic difficulty depends in part on the fact that early evidence of deficiences of several nutrients is related to abnormalities of function, and these functional disturbances can be mimicked by many conditions which are primarily psychogenic in their origin. It also depends in part on the fact that the anatomic lesions related by students of nutrition to the less severe degrees of malnutrition, lesions such as folliculosis of the skin, thickening of the conjunctiva and atrophy of the papillae of the tongue are not specific and hence not pathognostic in and by themselves.

The Board has further been disturbed by the lack of interest displayed by many physicians in this subject, a lack of interest which sometimes is accompanied by a strange credulity. This has led too frequently to prescribing vitamins as panaceas for illnesses and symptoms of many kinds, without regard to the great advances in our knowledge of the specific roles of vitamins and of human requirements for these and other nutrients. In the spotlight recently are protein hydrolysates, which have been employed by some physicians with almost equal lack of rationality.

In the opinion of the Board this handbook of "Clinical Nutrition" will serve the very useful purpose of disseminating current knowledge to physicians in a helpful form, thereby contributing to lessening the difficulties just mentioned.

A notable and most instructive feature of the book is the inclusion of many illustrations, in natural color, of manifestations of nutritional deficiencies in man.

The editors of this book are well known for their experience in nutrition. The responsibility for ideas expressed and statements made naturally rests with the authors of the several chapters, but these authors have been chosen with great care from well-known students of the several subjects covered and the chapters, therefore, carry the weight of their authority and special experience. The editors, authors, and the members of the Food and Nutrition Board sincerely hope that this volume will be helpful to physicians, medical teachers, and medical students, and through these to the many thousands whose health and vitality may be improved by better nutrition.

The royalties accruing from this book were assigned by the editors and authors to the Food and Nutrition Board. For this the Board is most appreciative. The editors and the Board wish to take this opportunity to express their gratitude to the National Vitamin Foundation for a generous financial contribution to cover the cost of the colored plates and for much of the expense of editing.

RUSSELL M. WILDER, M.D.
Vice-Chairman, Food and Nutrition Board

Preface

WE NOW know that proper nutrition, in addition to its role in the prevention and therapy of nutritional diseases, is both a major safeguard against future illness and one of the most valuable adjuncts to specific therapy when illness occurs. Thus the new nutritional knowledge now plays a role in every medical and surgical specialty as well as in general practice.

Nutrition is no longer the empiric science it once was. We have learned many new and important facts about the basic constituents of food and the clinical results of their deprivation or utilization. It is the purpose of this book to make the clinically significant portions of this new knowledge available in a form which the physician can apply in his daily practice, and the medical student can use in his studies.

The relationship of physiologic status and nutritional deficiency is twofold. Not only does nutritional abnormality often result in a diseased state but systemic disease, unrelated to nutrition, may precipitate a "conditioned" nutritional deficiency even though normal intake of nutrient continues. This concept may be traced throughout the book and receives special emphasis in the chapter devoted to the pathogenesis of deficiency syndromes.

In Part I, on diagnosis, the technics which may be useful clinically in the detection of deficiencies are described. There are chapters on practical laboratory aids and roentgen findings as well as on the interpretation of the dietary history and clinical signs. A method for a quick evaluation of the dietary pattern is provided, which makes it practical for the busy physician to estimate the nutrient intake without a long and detailed dietary history for which he has neither the inclination, time, nor patience. A section of natural color photographs is included here, illustrating the common, and many of the less common anatomic lesions associated with nutritional disease. It is hoped that these pictures will assist the physician and medical student in recognizing the clinical signs described in the later chapters on specific nutrients. The editors wish to acknowledge and thank the great number of physicians from all over the world who provided us with several thousand pictures from which these ninety were selected. We also wish to thank the National Vitamin Foundation, and its Scientific Director, Dr. Robert S. Goodhart, for the grant to the Food and Nutrition Board of the National Research Council, which made the expensive color reproduction of these pictures possible without increasing the price of the book.

The second and largest part of the book takes up the individual nutrients. Each nutritive element is discussed by an author who has devoted special study to his subject. These chapters are organized uniformly to present, first, a brief but clinically adequate description of the biochemistry; second, a consideration of the physiology of its utilization by the body; and then the requirements in health and disease, the results of deficiency, and treatment. The function of the trace elements and so-called "lesser vitamins" and their role in nutrition is described.

Part III is concerned with therapy and prevention. Extensive chapters are devoted to diet therapy of systemic disease. Here specific diet plans are given for particular clinical problems. In the chapter on obesity the evidence that the deposition of excess fat is the result of caloric excess is well documented and the low caloric diets used in treatment are fully described. There are full discussions of the available evidence concerning the relationship of the nutritional status of the individual to his ability to work under a variety of abnormal conditions, as well as to his resistance to toxic chemicals.

For the reader's convenience tables which might have been repeated in various chapters have been assembled in the Appendix. Among the reference tools to be found there is a selection of nineteen dietary patterns, adequate in all nutrients, which may be used as the basis of intelligent menu planning. These include diets for children, the aged, pregnant, and those of various national and regional food habits. There is also a table of food values, in which the nutritional composition of over 250 common food items are presented.

An effort has been made to include that which is clinically significant or may become so in the near future and to omit that which is of purely academic interest. We are aware that errors and oversights have undoubtedly occurred and hope that these will be called to our attention so that they may be taken into account should subsequent editions be called for.

The editors wish to thank each of the individual contributors to this volume, for each contribution represents many, many hours of painstaking writing, revision, and re-writing taken from a busy professional life. Their remunerations can only be their own satisfaction in making their special knowledge available to others. The editors wish also to thank them for permitting the editorial changes essential for uniform presentation (particularly in Section II).

The editors wish to take this opportunity to thank and to acknowledge our appreciation to many people who have given advice and constructively criticized the individual chapters of this volume. Special thanks are due to Dr. Elmer Alpert for preparation of the index, the appendix, and for proof reading; to Miss Ruth Abramson for many retypings while still in manuscript form and for help in proof reading; and to the publishers for their endless patience with us as well as for their numerous suggestions and criticisms.

The Editors

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Part I

DIAGNOSIS OF NUTRITIONAL DEFICIENCY

Chapter 1

THE PATHOGENESIS OF DEFICIENCY DISEASE

Norman Jolliffe

A NUTRITIONAL deficiency disease is caused by a nutritional inadequacy. Nutritional inadequacy results whenever adequate amounts of essential nutrients are not provided to tissues which require them for normal functioning. Nutritional inadequacy may be caused, first, by a dietary inadequacy. This type is known as primary nutritional inadequacy. Nutritional inadequacy may also result from various environmental conditions and bodily states that interfere with ingestion, absorption, or utilization of essential nutrients, or from factors that increase the requirement or cause the destruction or abnormal excretion of these nutrients. This type of nutritional inadequacy is secondary or conditioned. Between the occurrence of a nutritional inadequacy, primary or conditioned, and the onset of nutritional disease, time elapses. The time may be short or long, depending on the amount of nutrient reserve and the degree of nutritional inadequacy. But when the nutrient reserves are sufficiently exhausted tissue depletion occurs. Tissue depletion is followed in succession by biochemical "lesions," functional changes and, finally, anatomic lesions. No step in this chain of events is necessarily complete before the next begins. This, in brief, is the pathogenesis of nutritional deficiency diseases. It is outlined in Figure 1.

PRIMARY NUTRITIONAL INADEQUACY

Dietary or primary nutritional inadequacy has probably existed in some part of the world population ever since recorded history began. It is especially prevalent after crop failures and during and following wars. The pressure of peoples to obtain and insure dietary adequacy has been a frequent cause of mass migrations and of war. Mild dietary inadequacies have provoked peoples either to rebellion or to heroic group effort, depending upon motivation and leadership. Severe dietary inadequacies have made people angry, submissive, listless, disease ridden and incapable of productive work, resistance or, finally, of continuing to live. Entire population groups reduced to the listless stage have subsisted for generations with chronic dietary inadequacies sufficient to progressively lower their work output, which, with high fecundity, results in a constantly diminishing per capita food supply.

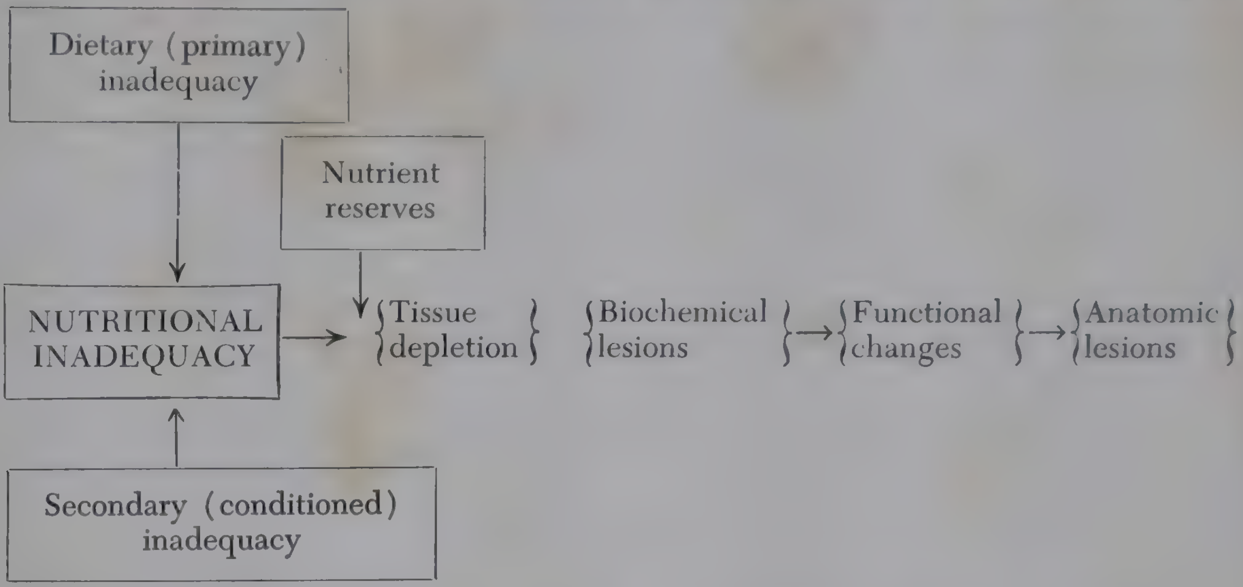
Dietary (primary) inadequacy
Nutrient reserves
NUTRITIONAL INADEQUACY
Tissue depletion
Biochemical lesions
Functional changes
Anatomic lesions
Secondary (conditioned) inadequacy

Fig. 1. Schema of the pathogenesis of nutritional deficiency diseases.

Nutritive Composition of the Food Supply of the United States

In contradistinction to many nations of the world, the nutritive composition of the food supply of the United States has been among the best. The per capita nutrient supply since 1910, after conservative deductions for losses in transportation, storage, and cooking are estimated in Table 1. Per capita nutrient values below the National Research Council's weighted Recommended Allowances are in *italicized* type to facilitate rapid evaluation. A glance is sufficient to indicate that since 1943 all nutrients except calcium have been in excess of the weighted Recommended

TABLE 1. ESTIMATED* NUTRITIVE VALUE OF CIVILIAN FOOD SUPPLY

(EXPRESSED AS DAILY QUANTITIES OF NUTRIENTS PER CAPITA AFTER ALLOWANCES FOR WASTE AND DETERIORATION OF INGREDIENTS IN STORAGE, TRANSPORTATION, COOKING AND LEECHING LOSSES)

Year	*Energy* Calories	*Protein* Gm.	*Fat* Gm.	*Carbo-hydrate* Gm.	*Calcium* Gm.	*Iron* Mg.	*Vitamin A* I. U.	*Thiamine* Mg.	*Ribo-flavin* Mg.	*Niacin* Mg.	*Ascorbic acid* Mg.	*Remarks*
1910	3180	93	113	450	*0.76*§	12.2	6550	*1.07*	*1.68*	*12.3*	74	
1915	3120	90	115	440	*0.77*	11.7	6550	*1.06*	*1.67*	*11.6*	74	
1920	3080	89	114	430	*0.81*	12.0	6900	*1.03*	*1.70*	*11.5*	75	
1925	3150	87	123	430	*0.80*	*11.6*	6370	*1.03*	*1.70*	*11.4*	72	
1930	3190	86	124	440	*0.83*	*11.6*	6640	*1.05*	*1.74*	*11.1*	70	
1935–1939 Av.	2980	84	121	400	*0.86*	*11.5*	7170	*0.98*	*1.74*	*10.9*	80	
1940	3060	86	132	390	*0.88*	11.8	7170	*1.07*	1.81	*11.4*	84	
1941	3130	88	132	410	*0.91*	12.2	7350	*1.12*	1.85	*12.1*	85	
1942	3080	90	128	400	*0.95*	13.3	7970	*1.24*	1.94	*12.3*	90	
1943	3130	94	131	400	*0.98*	14.1	8140	1.41	2.08	13.8	88	
1944	3130	93	132	400	*0.98*	15.2	8230	1.42	2.31	15.0	94	
1945	3170	97	129	390	1.03	15.5	8670	1.41	2.39	15.4	97	
1946	3110	99	134	390	1.06	15.8	8400	1.48	2.41	15.4	96	
1947	3080	92	132	390	*1.00*	14.9	7790	1.34	2.28	14.6	91	
1948	2980	90	130	375	*0.97*	14.0	7700	1.29	2.17	13.7	86	
Weighted NRC† Allowances	2600	65	—	—	1.01	11.7	4560	1.28	1.76	12.8	70	

---

* Calculated from Table 39 of *Nutrients available for consumption per capita per day, 1909–1948*, Miscellaneous Publication 691, U.S. Dept. of Agriculture, Aug. 1949. This tables gives the edible nutrients available for civilian consumption at the retail level including estimates of food supplied by farm and city gardens. No deductions were made in the nutrient estimates for the loss or waste or destruction of nutrients during the home preparation of food. These losses have been estimated for each of the years by applying the same deductions as were made by the War Food Administration in the 1944 food supply (personal communication from Charlotte Chatfield, Chief, Food Needs Section, Civilian Food Requirement Branch, Office of Marketing Services, War Food Administration. These figures represent 92.1% of calories, 94.0% of protein, 92.0% of fat, 93.0% of carbohydrate and calcium, 82.5% of iron, 88.5% of vitamin A, 63.0% of thiamine, 92.5% of riboflavin, 70.5% of niacin, and 70.0% of ascorbic acid. These levels do not include nutrients discarded into the garbage.

† From Table 13, Miscellaneous Publication 616, U. S. Dept. of Agriculture, 1947.

§ Italicized numbers represent nutrient levels below weighted allowances.

Allowances, the supply ranging from an insignificant deficit for calcium, the nutrient in shortest supply, to an excess of about 85 per cent for vitamin A, the nutrient in most abundant supply. Corresponding values for the excess in other nutrients are: calories, 20 per cent; protein, 45 per cent; iron, 25 per cent; thiamine, 10 per cent; riboflavin, 25 per cent; niacin, 10 per cent; and ascorbic acid, 25 per cent. Although on a per capita basis all nutrients except calcium have exceeded the weighted Recommended Allowances since 1943, in only three categories, calories, protein, and vitamin A, has our food supply since 1910 consistently provided a margin of safety. Every other nutrient tabulated, at some time or another, has failed to supply these allowances.

The supply of calcium was short for every year except 1945 and 1946, at which time the steady rise in milk consumption, which furnishes about 75 per cent of our calcium, provided a sufficient supply to meet the weighted Recommended Allowance on a per capita basis. The slight reduction in our milk supply since then has wiped out our small margin over the weighted Recommended Allowance of calcium in 1945 and 1946.

The per capita supply of iron declined from 1910 to 1940, falling to slightly below the weighted Recommended Allowance in the period 1925 to 1939. This decline reflected the decrease in consumption of grain and meat products over that period, and the increase since 1940 reflects a rising consumption of these products as well as the enrichment of bread and flour.

The per capita supply of thiamine was short of the weighted Recommended Allowances prior to 1943. From 1910 to 1940 it averaged only 80 per cent, and in the period 1935–39 only 76 per cent, of the weighted Recommended Allowances. The progressive fall in thiamine consumption from 1910 to the low 1935–39 average was due to the decline in grain and meat consumption and the increase in sugar consumption, both superimposed upon high milling of wheat which resulted in the removal of about 90 per cent of its thiamine. The rise in per capita consumption of thiamine since 1940 is a reflection partly of the increased consumption of meat, but chiefly of the bread and flour enrichment program.

The per capita supply of riboflavin was somewhat below the weighted Recommended Allowances prior to 1940, averaging about 95 per cent of this allowance. The gradual increase in the per capita intake of riboflavin from 1910 to 1943 was due almost entirely to the increased consumption of milk. Since 1943 the increase in milk consumption has continued and, in addition, bread and flour enrichment has added an additional margin over the weighted Recommended Allowances.

The per capita supply of niacin was short of the weighted Recommended Allowances prior to 1943, averaging about 85 per cent of this

TABLE 2. CONTRIBUTION OF BREAD AND FLOUR ENRICHMENT TO ESTIMATED MG. PER CAPITA FOOD SUPPLY OF IRON, THIAMINE, RIBOFLAVIN, AND NIACIN

Year	*Iron*			*Thiamine*			*Riboflavin*			*Niacin*		
	After Enrichment Mg.*	Before Enrichment Mg.†	Supplied by Enrichment† %	After Enrichment Mg.*	Before Enrichment Mg.†	Supplied by Enrichment† %	After Enrichment Mg.*	Before Enrichment Mg.†	Supplied by Enrichment† %	After Enrichment Mg.*	Before Enrichment Mg.†	Supplied by Enrichment† %
1935–1939 Average	*11.5*	*11.5*	0	*0.98*	*0.98*	0	*1.74*	*1.74*	2	*10.9*	*10.9*	0
1940	11.8	11.8	0	*1.07*	*1.07*	0	1.81	1.81	2	*11.4*	*11.4*	0
1941	12.2	11.8	3	*1.12*	*1.03*	8	1.85	1.81	2	*12.1*	*11.6*	4
1942	13.3	12.2	8	*1.24*	*1.02*	18	1.94	1.88	3	*12.3*	*12.0*	3
1943	14.1	12.5	11	1.41	*1.05*	26	2.08	1.97	5	13.8	*12.3*	11
1944	15.2	12.5	18	1.42	*1.06*	25	2.31	2.00	13	15.0	*12.2*	19
1945	15.5	13.0	16	1.41	*1.04*	26	2.39	2.03	15	15.4	*12.5*	19
1946	15.8	12.9	18	1.48	*1.05*	29	2.41	2.10	13	15.4	*12.2*	21
1947	14.9	12.5	16	1.34	*1.00*	25	2.28	1.98	13	14.6	*12.4*	15
1948	14.0	12.3	12	1.29	*0.97*	25	2.17	1.94	11	13.7	*11.5*	16
Weighted NRC Allowances**		11.7			1.28			1.76			12.8	

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* From Table 1.

† From Table 8, Miscellaneous Publication 616, U.S. Dept. of Agriculture, 1947. Figures for 1946, 1947, and 1948 estimated to be the same as 1945.

‡ Italicized numbers represent nutrient levels below weighted allowances.

**See footnote †, Table 1.

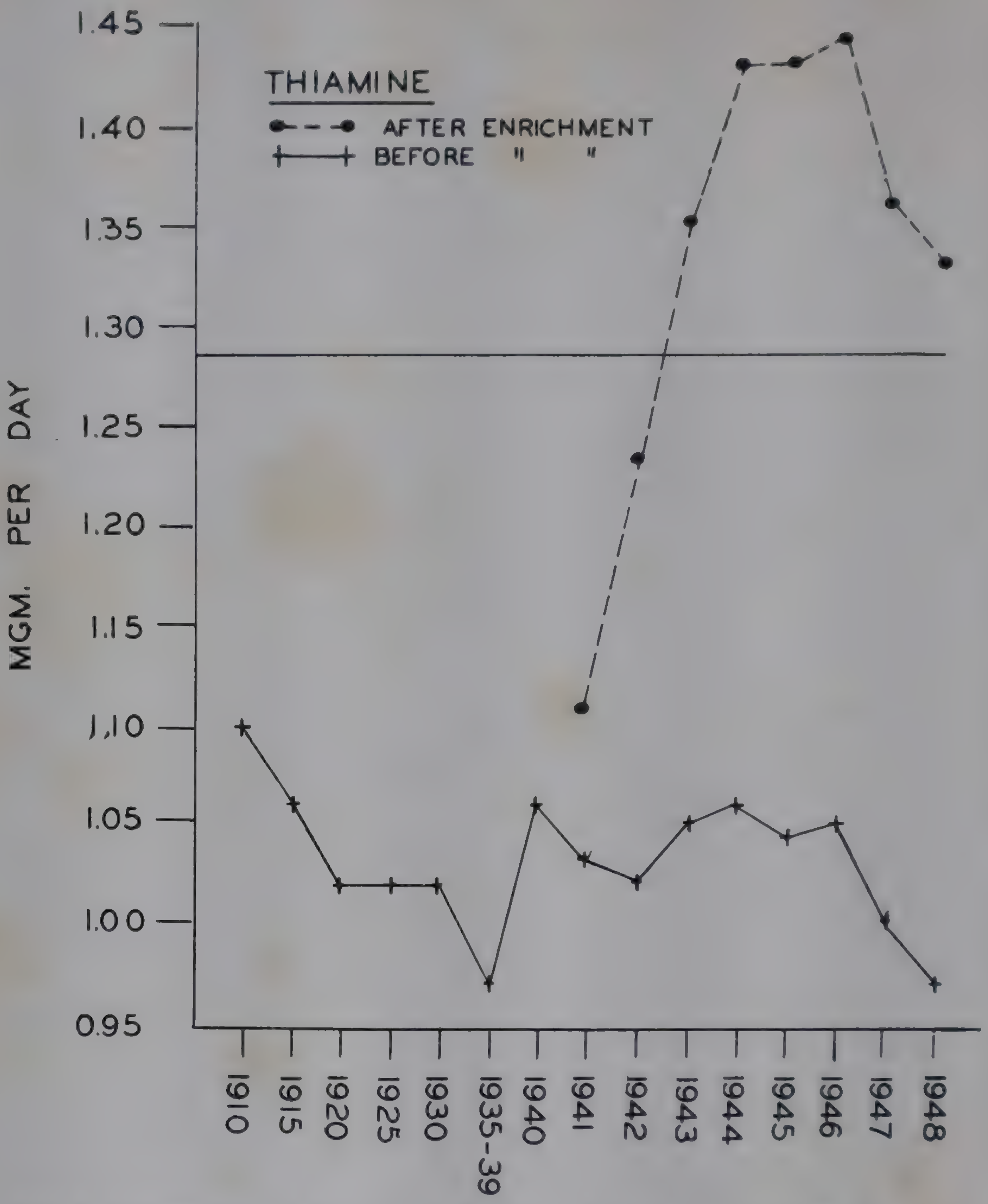

FIG. 2. Contribution of bread and flour enrichment to estimated per capita food supply of thiamine. Data from Table 2.

allowance between 1910 and 1940. The fall in niacin consumption from 1910 to the low 1935–39 average reflected the decreasing consumption of meat during this period. The rise in per capita consumption of niacin since 1940 is a reflection partly of the increased meat consumption, but is chiefly due to the bread and flour enrichment program.

Prior to the 1935–39 average, the per capita supply of ascorbic acid was slightly above the weighted Recommended Allowances. The rise in the per capita supply of ascorbic acid in recent years has been due partly to the increased consumption of citrus fruits and tomatoes, and partly to the increased use of fresh vegetables from wartime gardens.

The contribution of the bread and flour enrichment program to the per capita nutrient supply of iron, thiamine, riboflavin, and niacin is shown in Table 2. As in the preceding table, the per capita nutrients in short supply, as compared to the weighted Recommended Allowances, are in *italicized* type. Inspection of these tables shows that without the enrichment of bread and flour both thiamine and niacin would still be significantly short of the weighted Recommended Allowances, amounting to a deficit of 18 per cent for thiamine and of 5 per cent for niacin during 1946. These data are presented graphically in Figures 2 and 3. It is the critical change in the dietary intake of niacin and thiamine that probably accounts for the sudden dearth of patients with florid pellagra on the wards of charity hospitals since 1942. It thus seems that the 27 per cent of our total per capita supply of thiamine and the 19 per cent of our total per capita supply of niacin furnished by the chemical industry through bread and flour enrichment has played an important public health role in this country. Although the chemical industry provides through bread and flour enrichment about 17 per cent of the per capita supply of iron and 12 per cent of the per capita supply of riboflavin, these two factors have not been of the same critical importance as the industry's supply of thiamine and niacin. Both iron and riboflavin, on a per capita basis, would have met the weighted Recommended Allowances without enrichment (see Figs. 4 and 5). However, the margin of safety of about 33 per cent in these two nutrients, provided by the enrichment program, is the level which should be aimed at in the per capita consumption of thiamine, riboflavin, and calcium.

The available per capita supply of nutrients in America's food is sufficient, with equitable distribution, to meet the needs of the people as measured by the Recommended Dietary Allowances. It is not reasonable, however, to assume that perfect distribution has ever been or can be attained. The number of people who received both more and less than the available average must be large. In addition, only very conservative deductions were made for waste, deterioration of ingredients in storage and transportation, and cooking losses, and no deductions were made for nutrient losses after the dinner plate was reached. In some frugal families this latter loss is not large, but in many it is considerable. In some households the cooking and leeching losses may be kept within the conservative deductions applied, but in many families these losses are greater and the figures used should be considered as goals rather than as true estimates

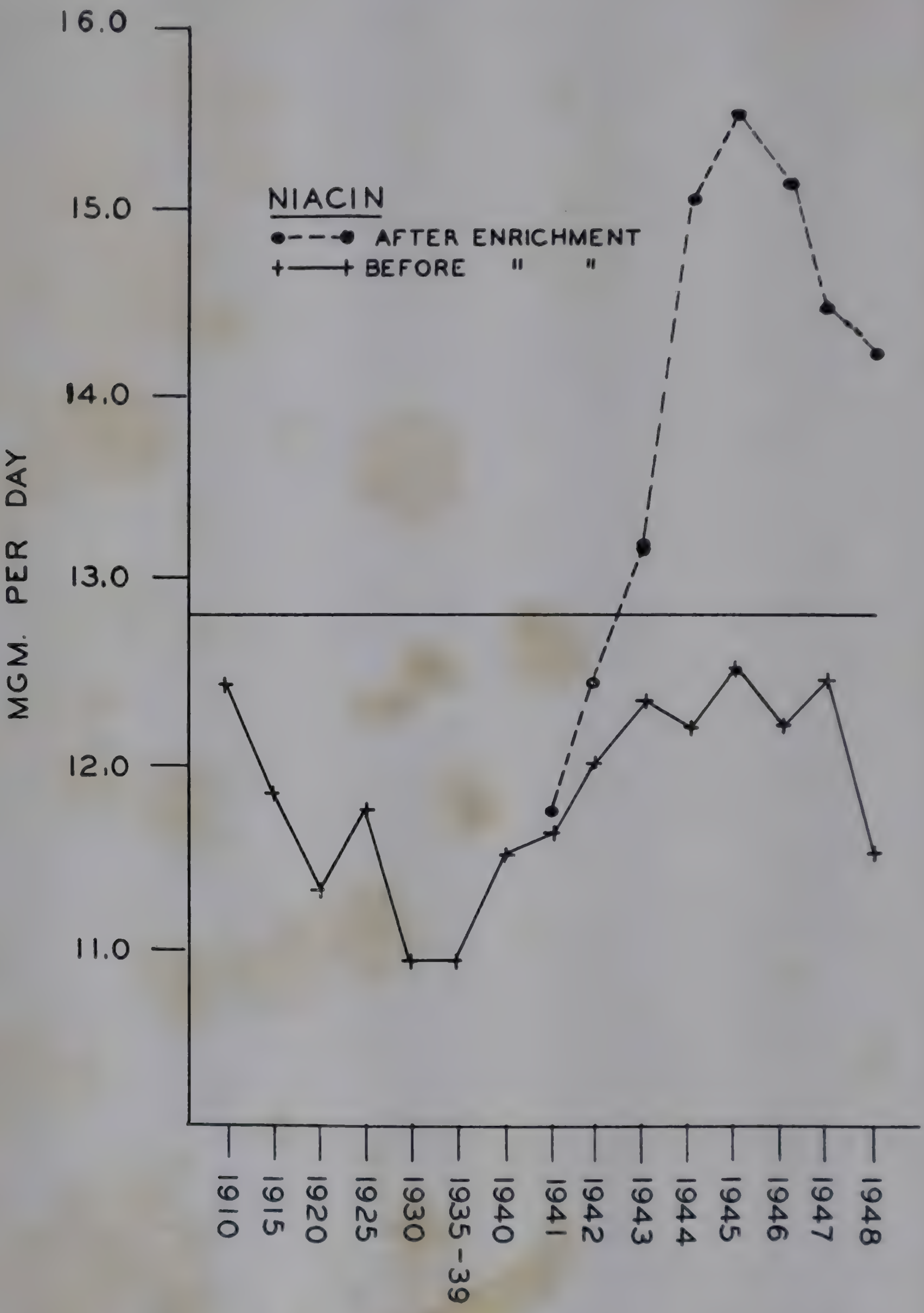

FIG. 3. Contribution of bread and flour enrichment to estimated per capita food supply of niacin. Data from Table 2.

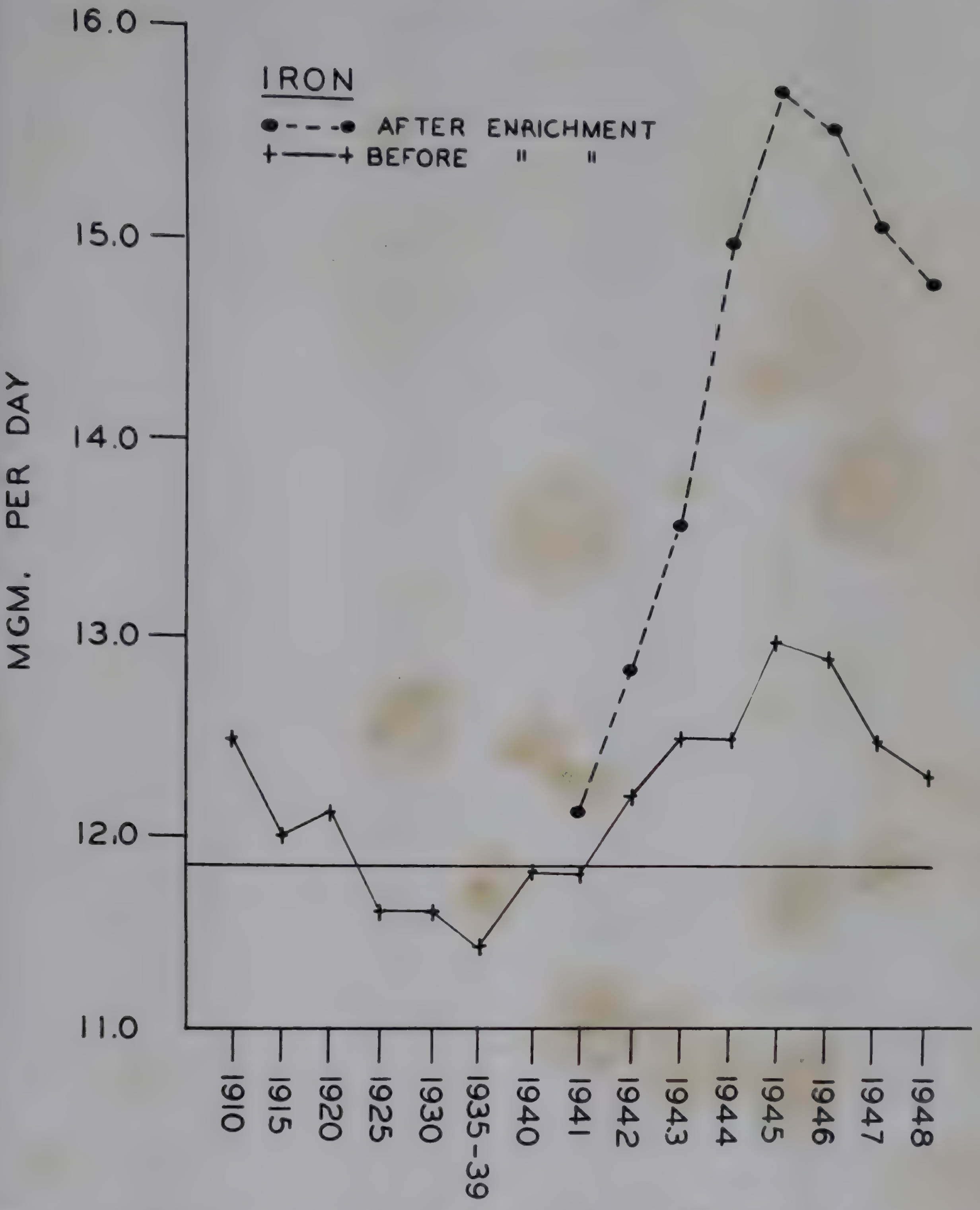

FIG. 4. Contribution of bread and flour enrichment to estimated per capita food supply of iron. Data from Table 2.

of nutrient losses. The figures, then, for the per capita amounts of nutrients in our food supply are generous and probably represent the most that can be obtained.

The National Research Council's Recommended Dietary Allowances are considered by many people as too liberal in that they represent levels considerably above the average requirements. For example, careful study of the minimum requirements of thiamine by healthy normal adults has shown the requirement to vary from 0.15 to 0.45 mg. per thousand calories, with the average in the order of 0.30 to 0.40 mg. per thousand calories. The N.R.C. allowances of thiamine have been calculated on the basis of about 0.5 mg. per thousand calories, giving 1.2 mg. of thiamine for a normal adult consuming a 2500-calorie diet, and 1.5 mg. for a normal adult diet of 3000 calories. If the average thiamine requirement of about 0.35 mg. per thousand calories had been taken as a satisfactory allowance, and this allowance were used in supplying food to a population, that proportion of the population having requirements over 0.35 mg. per thousand calories would eventually suffer from thiamine deficiency. Since the individual has no way of knowing whether his needs are average, or below or above average, and since those responsible for feeding groups have no practical way of identifying or segregating those with non-average requirements, the only nutrient levels that can be countenanced are those that provide enough for all well persons whether their requirements, compared to the average, are high or low. It is for this reason that the recommended allowances include a factor of safety of about 30 per cent above the average minimum requirement.[30]

The failure of an individual or a group of persons to consume dietaries meeting the N.R.C. allowances does not mean that any one individual has an inadequate diet. It does mean, however, that the group diet is unsatisfactory in that it fails to provide adequate nutrients for some persons whose requirements are in excess of their dietary intake.[15]

Another factor justifying the use of the National Research Council's Recommended Dietary Allowances rather than minimum requirements is that much controversy exists concerning the minimum amounts of the various nutrients that are needed to avoid dietary inadequacies and the resulting deficiency diseases. In contrast there is fair unanimity that the National Research Council's Recommended Dietary Allowances represent approximately the amounts of essential nutrients needed by population groups to insure everything that food can contribute toward the long range advancement of human welfare. The Journal of the American Medical Association has noted editorially "that there is a real difference as measured in terms of growth, development and general health record between optimum and just adequate nutrition; and that every practical effort should be made to apply this knowledge in the interests of human welfare."[4]

It seems, therefore, that the nutrients contained in the food supply of the United States are adequate compared with the N.R.C. Recommended Allowances but that this supply, even with equitable distribution, must

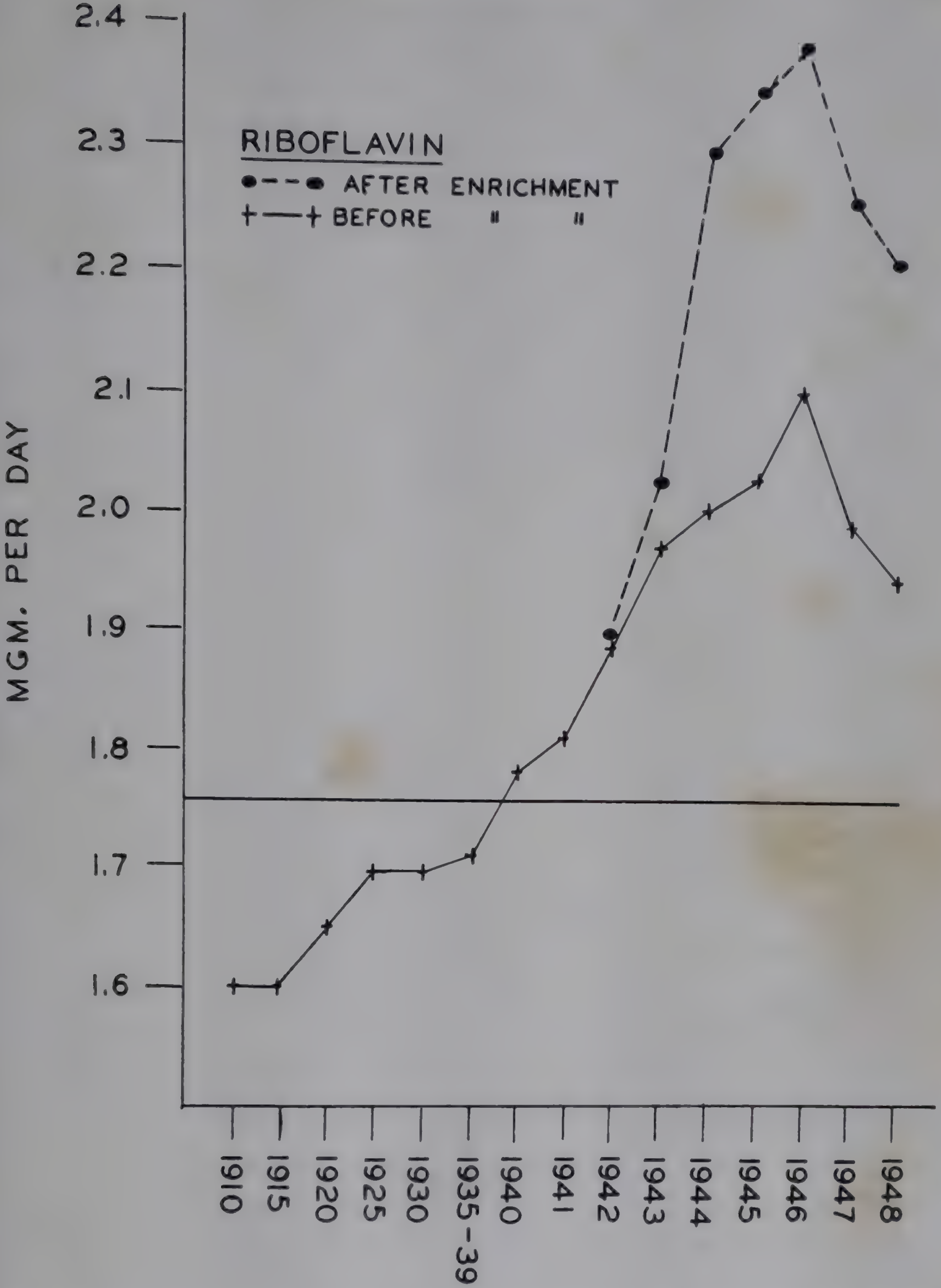

Fig. 5. Contribution of bread and flour enrichment to estimated per capita food supply of riboflavin. Data from Table 2.

be transported, cooked, and served with frugality lest there be an actual per capita deficit, especially in the more fragile nutrients.

All the evidence from numerous surveys during the past ten years among persons of all ages in many localities is in complete agreement that unsatisfactory diets are widespread throughout the nation. This was the conclusion of a committee of the Food and Nutrition Board of the National Research Council reporting in November, 1943.[4]

There is no need to present here all the evidence presented by that committee. Their tables showing the percentages of persons with intakes of dietary essentials at less than 100, 75, 50, and 25 per cent of the recommended levels are reproduced in Tables 3 to 6. Whether the full N.R.C. dietary allowances are insisted on as essential, or 75 per cent or 50 per cent of these levels are taken as satisfactory, the evidence remains qualitatively the same: there was a widespread prevalence of unsatisfactory diets in the United States in the early years of the present decade. Even if it is assumed that 25 per cent of the N.R.C. dietary allowances would be satisfactory there still remains a substantial proportion of unsatisfactory diets.

Surveys made still more recently have shown some improvement, reflecting the gains in the per capita nutrient supply as well as the greater purchasing power of the people. For example, the Bureau of Human Nutrition and Home Economics[27] reported in 1944 that

> . . . in 1936 about three fourths of the families in the United States had diets that did not meet the National Research Council's recommendation for riboflavin: and about half had diets that were low in calcium, thiamine and ascorbic acid. It is estimated that in the spring of 1942 the diets of more than half of the families still did not meet the recommended allowances for riboflavin and that the proportion of diets low in calcium had been reduced to less than a third; the proportion low in thiamine to a fourth, and the proportion low in ascorbic acid, in which there was the greatest improvement, to less than a tenth. Some of the improved situation in respect to ascorbic acid was a result of seasonal increases in the consumption of citrus fruit and leafy greens. There was also a great reduction in the estimated proportion of families that had diets failing to meet current recommendations in Vitamin A value, iron and protein, from about a fourth in the earlier period to around a tenth in the later period.

The American Institute of Public Opinion[7] in February, 1943, made a single-day survey of consumption of the seven groups of foods considered essential in a satisfactory diet as recommended by the Bureau of Human Nutrition and Home Economics. The results of this survey show that a significant fraction of the American population in all economic groups fails to include all the basic foods in the daily diet. As will be pointed out (Chapter 2) this means that the diet is probably unsatisfactory.

TABLE 3. PERCENTAGES OF PERSONS WITH INTAKE OF THE RESPECTIVE DIETARY ESSENTIALS AT LESS THAN RECOMMENDED LEVELS

Essential nutrients	*Wilkes-Barre, Pa.*			*Lancaster Co., Pa.*			*New York, N. Y.*			*Wilson Co., Tenn.*							*Philadelphia, Pa.*		*Wayne Co., N. C.*	
	748 white children 1-12 yrs., 1937	39 white school adolescents 13-20 yrs., 1937	14 colored children 1-12 yrs., 1937	42 white children 1-12 yrs., 1938-40	20 white adolescents 13-20 yrs., 1938-40	38 white adults, 1938-40	2,037 high school pupils 1939-40	293 private high school pupils, 1939-40	Chatham County, North Carolina,[24] 110 white adults, 1940-41	457 white adults, 1941	194 colored adults, 1941	113 white adolescents, 1941	76 colored adolescents, 1941	206 white infants and children, 1941	115 colored infants and children, 1941	Burbank, California,[24] 250 aircraft workers, 1941-42	562 white children 1-12 yrs., 1941-42	38 white school adolescents 13-20 yrs., 1941-42	56 white, 15 yrs. and over, summer, 1942	39 colored, 15 yrs. and over, summer, 1942
Calories	93	100	100	36	30	87	74	68	—	82	95	89	100	69	95	78	90	93	—	—
Protein	81	100	92	21	20	8	44	26	83	51	74	78	94	61	87	15	58	71	55	59
Calcium	92	100	100	64	70	24	72	61	84	61	77	87	93	77	99	48	71	100	86	82
Iron	81	97	92	17	20	10	64	36	82	59	69	84	89	70	83	22	53	71	66	79
Vitamin A	67	85	54	33	45	37	65	35	70	45	48	60	59	45	51	42	42	71	62	72
Thiamine	74	100	85	36	45	84	53	18	99	94	98	93	96	79	93	46	60	64	91	90
Riboflavin	99	100	100	81	90	97	70	36	97	91	99	85	97	55	91	71	53	64	100	97
Niacin	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	30	97	86	—	—
Ascorbic acid	71	95	85	24	30	5	58	20	84	52	62	68	73	67	70	67	52	71	93	92

TABLE 4. PERCENTAGES OF PERSONS WITH INTAKE OF THE RESPECTIVE DIETARY ESSENTIALS AT LESS THAN 75 PER CENT OF RECOMMENDED LEVELS

	Wilkes-Barre, Pa.			*Lancaster Co., Pa.*			*New York, N. Y.*			*Wilson Co., Tenn.*							*Philadelphia, Pa.*		*Wayne Co., N. C.*	
Essential nutrients	748 white children 1–12 yrs., 1937	39 white school adolescents 13–20 yrs., 1937	14 colored children 1–12 yrs., 1937	42 white children 1–12 yrs., 1938–40	20 white adolescents 13–20 yrs., 1938–40	38 white adults, 1938–40	2,037 high school pupils 1939–40	293 private high school pupils, 1939–40	Chatham County, North Carolina,[23, 24] 110 white adults, 1940–41	457 white adults, 1941	194 colored adults, 1941	113 white adolescents, 1941	76 colored adolescents, 1941	206 white infants and children, 1941	115 colored infants and children, 1941	Burbank, California,[34] 250 aircraft workers, 1941–42	562 white children 1–12 yrs., 1941–42	38 white school adolescents 13–20 yrs., 1941–42	56 white, 15 yrs. and over, summer, 1942	39 colored, 15 yrs. and over, summer, 1942
Calories	67	100	85	7	5	21	33	29	—	50	77	56	89	36	77	38	43	50	—	—
Protein	35	87	54	0	0	0	11	7	42	24	45	42	74	39	66	3	6	21	14	21
Calcium	69	95	100	33	25	13	38	32	63	43	61	65	75	58	90	32	39	71	61	69
Iron	42	90	54	0	0	0	29	12	52	30	44	55	69	44	60	6	10	50	29	46
Vitamin A	48	72	23	10	15	13	47	22	46	32	42	42	47	30	43	22	19	50	43	59
Thiamine	46	87	62	14	0	50	22	4	98	78	91	76	89	51	80	22	23	36	77	82
Riboflavin	95	100	100	55	75	76	36	10	90	75	93	63	86	39	77	51	25	50	95	92
Niacin	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	12	66	71	—	—
Ascorbic acid	51	79	85	7	10	0	36	7	80	38	50	56	55	54	53	54	33	50	86	80

TABLE 5. PERCENTAGES OF PERSONS WITH INTAKE OF THE RESPECTIVE DIETARY ESSENTIALS AT LESS THAN 50 PER CENT OF RECOMMENDED LEVELS

	Wilkes-Barre, Pa.			*Lancaster Co., Pa.*			*New York, N. Y.*			*Wilson Co., Tenn.*							*Philadelphia, Pa.*		*Wayne Co., N. C.*	
Essential nutrients	748 white children 1–12 yrs., 1937	39 white school adolescents 13–20 yrs., 1937	14 colored children 1–12 yrs., 1937	42 white children 1–12 yrs., 1938–40	20 white adolescents 13–20 yrs., 1938–40	38 white adults, 1938–40	2,037 high school pupils 1939–40	293 private high school pupils, 1939–40	Chatham County, North Carolina,[21, 24] 110 white adults, 1940–41	457 white adults, 1941	194 colored adults, 1941	113 white adolescents, 1941	76 colored adolescents, 1941	206 white infants and children, 1941	115 colored infants and children, 1941	Burbank, California,[34] 250 aircraft workers, 1941–42	562 white children 1–12 yrs., 1941–42	38 white school adolescents 13–20 yrs., 1941–42	56 white, 15 yrs. and over, summer, 1942	39 colored, 15 yrs. and over, summer, 1942
Calories	22	64	38	2	0	5	4	4	—	12	40	11	42	12	45	4	4	7	—	—
Protein	6	36	8	0	0	0	1	0	10	7	18	13	33	12	35	0	1	0	2	10
Calcium	35	79	31	5	0	0	9	7	34	23	40	43	45	39	70	11	10	43	25	38
Iron	9	54	24	0	0	0	4	2	8	7	17	16	32	9	24	0	1	0	5	18
Vitamin A	24	49	15	0	0	8	20	8	27	15	32	19	37	18	34	3	7	14	27	44
Thiamine	15	54	23	0	0	0	3	1	74	31	65	29	55	23	47	6	2	7	43	46
Riboflavin	72	100	85	19	20	24	9	2	71	50	77	41	62	21	52	22	2	21	79	82
Niacin	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	25	43	—	—
Ascorbic acid	27	54	23	2	0	0	15	2	72	21	35	29	42	28	34	33	13	21	77	69

TABLE 6. PERCENTAGES OF PERSONS WITH INTAKE OF THE RESPECTIVE DIETARY ESSENTIALS AT LESS THAN 25 PER CENT OF RECOMMENDED LEVELS

Essential nutrients	*Wilkes-Barre Pa.*			*Lancaster Co., Pa.*			*New York, N. Y.*			*Wilson Co., Tenn.*							*Philadel-phia Pa.*		*Wayne Co. N. C.*	
	748 white children 1–12 yrs., 1937	39 white school adolescents 13–20 yrs., 1937	14 colored children 1–12 yrs., 1937	42 white children 1–12 yrs., 1938–40	20 white adolescents 13–20 yrs., 1938–40	38 white adults, 1938–40	2,037 high school pupils 1939–40	293 private high school pupils, 1939–40	Chatham County, North Carolina,[23, 24] 110 white adults, 1940–41	457 white adults, 1941	194 colored adults, 1941	113 white adolescents, 1941	76 colored adolescents, 1941	206 white infants and children, 1941	115 colored infants and children, 1941	Burbank, California,[34] 250 aircraft workers, 1941–42	562 white children 1–12 yrs., 1941–42	38 white school adolescents 13–20 yrs., 1941–42	56 white, 15 yrs. and over, summer, 1942	39 colored, 15 yrs. and over, summer, 1942
Calories	0	5	0	0	0	0	0	0	—	3	12	3	10	5	21	0	0	0	—	—
Protein	0	0	0	0	0	0	0	0	1	0	4	1	4	3	13	0	0	0	0	0
Calcium	7	28	15	0	0	0	1	1	4	3	9	10	15	7	26	0	2	7	0	5
Iron	1	3	0	0	0	0	0	0	0	1	3	3	8	3	7	0	0	0	0	8
Vitamin A	4	18	8	0	0	0	2	1	9	4	17	5	25	5	20	0	0	0	7	21
Thiamine	1	8	0	0	0	0	0	0	17	5	14	3	13	4	6	0	0	0	5	15
Riboflavin	29	54	23	7	5	8	0	0	23	9	32	7	18	6	20	0	0	0	20	39
Niacin	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	2	0	—	—
Ascorbic acid	7	15	23	0	0	0	2	0	45	5	13	7	27	7	16	8	3	0	52	49

In a survey conducted during August, September, November, and December, 1943, by Lockhart and his associates[24] actual chemical analysis was made of duplicates of meals eaten by 71 individuals selected to obtain a distribution of age (above 5 years), sex, activity, and economic status similar to that of the nation as a whole. By these analyses the average daily intake was found to be satisfactory in ascorbic acid, calcium, and iron but unsatisfactory in thiamine, riboflavin, and niacin. Only 7 per cent of the subjects, however, received a satisfactory level of all the nutrients analyzed, and all of these were children; 79 per cent of all subjects received two thirds of the recommended allowances in all nutrients.

Concurrently with this chemical dietary analysis a one-day survey was made of the diets of 3336 persons in all parts of the United States. The quality of the food selection in this large group was definitely inferior to that of the 71 individuals whose diets were examined by chemical analysis. "Thus it is possible that the dietary intake of the nation at the time this study was made was even less adequate than that of the small group whose diets were analyzed."

It seems, therefore, that compared to the National Research Council's Recommended Allowances there is a high incidence of unsatisfactory diets in all sections of the country. A rough approximation would suggest that the prevalence of unsatisfactory diets is about 75 per cent in some groups and may reach 90 per cent. By the standards of those who consider the National Research Council Recommended Daily Allowances as too liberal but would accept about two thirds as satisfactory, approximately one fourth to one third of the diets surveyed are unsatisfactory. Even the prevalence of diets below bare subsistence levels, providing only one fourth of the full allowances, is dangerously frequent and exceeds by far the prevalence of many diseases which receive much publicity and generous public contributions for their study and amelioration.

Factors Contributing to High Prevalence of Unsatisfactory Diets

The factors mainly responsible for the widespread prevalence of unsatisfactory diets in the presence of a satisfactory per capita nutrient supply can be classified under three headings: poor food habits, excessive consumption of highly refined foods, and price rationing. None of these factors stands alone but each is inextricably interwoven with the others.

Poor food habits develop in part out of the economic factors which are expressed by the term "price rationing"; they also foster and are a part of the wide use of refined sugar and its products. While ignorance of the rules of good nutrition is fundamental in the causation of poor food habits, they are dependent in considerable degree on popular taste and social custom, factors which weigh heavily in accounting for the immoderate consumption of nutritionally inferior foods.

Poor food habits may be either negative or positive. The negative poor food habits include nonconsumption of satisfactory amounts of the protective foods. This is often due to failure to promote the taste for these protective foods during childhood, to local food customs, ethnically determined antipathies, and economic restrictions. In many instances it is due to faulty social conditioning, as when the adolescent boy stops drinking milk after his first late dance.

The positive poor food habits include the immoderate use of sugar, candy, sweetened carbonated beverages, and alcohol.

The daily per capita consumption of sugar in the United States averaged 510 calories during the 1935–39 period. This rose to 575 calories in 1941 but during the war years fell progressively to 400 calories in 1945 and 1946.* The annual consumption of sugar has returned to prewar levels now (1949) that the supply is adequate and wartime rationing has ended.

The amount of candy sold in the United States in 1939 was sufficient to furnish 90 calories per capita per day.[13] During the war years it fell to about 20 calories per capita per day and in 1946 it was about 30 calories per capita per day.†

From the amount of sugar allocated to the industry in 1946, it can be calculated that sweetened carbonated beverages supplied about 39 calories per capita per day.

The amount of alcohol consumed per capita of the population 15 years of age and older in 1936 was sufficient to furnish 81 calories per day. In 1945 this figure reached 122 calories per day.‡ Jellinek[9] has estimated the actual users of alcohol in 1945 as 60 per cent of the population 15 years of age and older, exclusive of armed forces overseas. On this basis the average person who uses alcohol consumes 216 calories of it each day. There has been a slight decrease in the average since 1945.

Thus poor food habits in 1946 accounted in non-alcohol-consuming persons for 400 calories per capita daily, or approximately one-sixth of the daily caloric intake. Alcohol-consuming persons used an average of some 200 additional calories, giving this group 600 calories per capita daily, or about one-fourth of the daily caloric intake. The return to prewar levels of sugar consumption has raised these figures by some 150 calories daily. The chief criticism of these calories, from a nutritional viewpoint, is that they either displace other calories which carry with them protein and micronutrients, and by this contribute to malnutrition, or add to the total caloric intake, producing overweight.

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* Calculations based on 103.4 lb. of sugar for 1935–39, 111 lb. in 1941, and 78 lb. in 1945 and 1946, taken from Table 15 in Report of Food Industry Council Sugar Committee, November, 1946.

† Estimated from sugar allocations to industrial users in Table 5 in Report of Food Industry Council Sugar Committee, November, 1946.

‡ These calculations were made for me by Mr. Mark Keller, Assistant Editor, *Quarterly Journal of Studies on Alcohol.*

Excessive consumption of highly refined foods, especially before bread and flour enrichment, has contributed enormously to the poor nutritional milieu in our country. It has already been indicated how this is bound up with poor food habits, with the fact that white bread and sugar are widely considered as social refinements, besides appealing to popular taste. Economic necessity, however, is also involved in promoting the use of these products, for they are the cheapest sources of calories and together furnish about 50 per cent of our calories. Far-reaching changes in the American dietary have resulted from changes in our bread and flour. Prior to 1880 our grain was milled almost entirely in local communities, by methods which retained most of the vitamins and minerals. The introduction of the patent milling process, by removing most of the germ and the bran shorts from the flour, rendered it much less susceptible to weevils and spoilage and consequently permitted centralization of the milling industry. Without the patent process flour would of necessity be milled near its consumption locale, for the temperatures prevailing in most parts of this country during the summer months would permit neither long shipment nor storage without refrigeration. This feature recommended itself to the millers and food distributors. The American people at the same time preferred the resulting white, cleaner, more uniform, and better tasting bread. The patent milling process, however, caused the removal of about 90 per cent of the thiamine and 70 to 85 per cent of the riboflavin, niacin, and iron. Other nutrients, not concentrated in the germ and the bran, were less affected. The removal of thiamine, riboflavin, niacin, and iron from flour resulted in less than satisfactory amounts per capita of thiamine, riboflavin, and niacin, with no margin of safety in iron (see Table 1). Under these conditions it was inevitable that the less well-fed sections of the population should manifest nutritional disease due to inadequacies of these nutrients. Although pellagra has been recognized as endemic in the southern United States since 1907 it was not till the 1930's that clinicians became aware that deficiencies in the B vitamins were by no means rare in other parts of the country.[11, 17, 31] These facts, through the leadership of the Food and Nutrition Board of the National Research Council and its Committee on Cereals, led the Food and Drug Administration in 1941 to establish official standards of identity for "enriched" flour and informal ones for enriched bread, permitting millers and bakers voluntarily to add specified amounts of thiamine, riboflavin, niacin, and iron to flour and bread. Later, after Pearl Harbor, the War Food Administration issued Food Order Number 1 making this enrichment compulsory for pan-baked white bread and rolls. With expiration of the wartime emergency powers, bread enrichment is no longer compulsory by federal regulation, but many states have passed legislation making enrichment of white bread and flour compulsory. Examination of Table 2 and Figures 2 and 5 should convince the most skeptical of the improvement in the American diet as a result of bread and flour enrichment. It is possibly the most important public health advancement since compulsory pasteurization of milk.

Equally far-reaching changes have also occurred in the American dietary as a result of our varying consumption of sugar. About 100 years ago our annual consumption of sugar was not more than 10 lb. per capita. Since the Civil War, and especially from 1910 until wartime sugar rationing, this increased progressively so that our prewar consumption of sugar was over 100 lb. per capita per year. During the war it diminished to 78 lb. per capita per year. Now that sugar rationing has been discontinued the expected increase in sugar consumption has resulted which will, it is expected, displace other foods that carry with them essential micronutrients.

The third important factor accounting for the widespread prevalence of unsatisfactory diets is price rationing, an element which constantly confronts all those interested in public health. Stated in simple terms it means that some of the people in our country have available, for expenditure on food, less than the minimum cost of a satisfactory diet. Like the other factors, price rationing does not stand alone but is a part of and a cause of poor food habits and the established use of immoderate amounts of sugar. Moreover, it is set within a framework of individual, group, and national resources and requirement, and of industrial, social, political and economic policies. For this reason, although this aspect of the nutrition problem belongs properly in the realm of the political economist, the physician and public health worker must always take it into account when advising the individual patient or in planning a nutritional program.[13]

CONDITIONED OR SECONDARY NUTRITIONAL INADEQUACIES

Under this heading[14] the secondary effects of illness resulting in nutritional inadequacies will be discussed. The terms malnutrition, nutritional deficiency disease, nutritional failure, beriberi, pellagra, scurvy, riboflavin deficiency, and the like, signify to many persons disorders arising solely from an inadequate diet. But all these may occur in the presence of dietary adequacy. These terms should denote a deficiency in the bodily tissues rather than in the diet. If the nutritional inadequacy is caused by factors other than an inadequate diet alone it is known as a conditioned or secondary inadequacy. Conditioned inadequacies are caused by factors that interfere with the ingestion, absorption, or utilization of essential nutrients, or by factors that increase their requirement, destruction, or excretion.

The importance of these conditioning factors as a cause of nutritional inadequacy has not been generally recognized. In surveys of the nutritional status of population groups there has been a tendency to neglect the causal role of these conditioning factors and to attribute all malnutrition to dietary inadequacies alone. On the other hand, the finding of clear-cut gross manifestations of deficiency disease caused by conditioning factors may lead to one of two errors: The first is to consider the lesion a manifestation of the original or conditioning disease, unrelated to nutritional inadequacy. The second, after recognizing the nutritional basis of the secondary manifestation, is to attribute the original or conditioning disease to nutritional inadequacy. Those making the first error ignore the existence of deficiency disease, while those making the second error attribute most deviations from normal health to nutritional inadequacy.

The prevention and treatment of these conditioned nutritional inadequacies are often the decisive factors in determining recovery after surgery and in many severe infections. Likewise, their prevention and treatment often decide the success of other therapeutic measures directed toward alleviating the conditioning disease. In addition, the comfort, length of life, and economic usefulness of many patients depend on adequate nutrition.

Following the definition of a conditioned nutritional inadequacy, the various illnesses and conditions that may produce such inadequacies are listed in Table 7. It must be emphasized that this table is not complete. It is intended merely to list the more common illnesses, therapeutic measures, and physiologic alterations which condition the production of a nutritional inadequacy.

Interference with Ingestion

Strictly speaking, a nutritional inadequacy produced by interference with ingestion should not be considered as conditioned. Since failure to ingest adequate amounts of food is alone responsible, it would be reason-

Table 7. CONDITIONING FACTORS

I. Factors interfering with ingestion
  1. *Gastrointestinal disorders*
     Acute gastroenteritis, gallbladder disease, peptic ulcers, diarrheal diseases, and obstructive lesions of gastrointestinal tract
  2. *Neuropsychiatric disorders*
     Neurasthenia, neurosis, psychoneurosis, psychosis, migraine, and neurologic disorders interfering with self-feeding
  3. *Anorexia*
     Alcoholism, operations, anesthesia, infectious diseases, congestive heart failure, thiamine deficiency, visceral pain
  4. *Food allergy*
  5. *Loss of teeth*
  6. *Pregnancy*
  7. *Therapy*
     Diets restricting ingestion of essential foods

II. Factors increasing nutritive requirement
  1. *Abnormal activity*, as associated with:
     Prolonged strenuous physical exertion, delirium, and certain psychoses
  2. *Abnormal environmental factors*
     Excessively high temperatures, as in the tropics, in deserts and in certain industries
     Excessive light glare as from snow or klieg lights
  3. *Fever*
  4. *Hyperthyroidism*
  5. *Pregnancy and lactation*
  6. *Therapy* such as thyroid, alpha-dinitrophenol, parenteral dextrose solutions, fever therapy, high carbohydrate diets

III. Factors interfering with absorption
  1. *Gastrointestinal diseases* associated with hypermotility or reduction of absorbing surfaces
  2. *Achlorhydria*
  3. *Biliary disease*, especially obstructive jaundice
  4. *Vitamin deficiency*
  5. *Therapy*
     Liquid petrolatum, colloidal adsorbents, severe catharsis, gastric or intestinal resections, and short-circuiting operations

IV. Factors interfering with utilization
  1. *Hepatic dysfunction*, as in:
     Liver disease, diabetes mellitus, alcoholism
  2. *Hypothyroidism*
  3. *Malignancy*
  4. *Therapy*
     Sulfonamide drugs, radiation, therapy, phenytoin

V. Factors increasing excretion
  1. *Polyuria*, as in:
     Diabetes mellitus, diabetes insipidus
  2. *Lactation*
  3. *Excessive perspiration*
  4. *Therapy*
     Long continued excessive fluid intake, as in urinary tract infections

VI. Factors increasing destruction
  1. *Achlorhydria*
  2. *Lead poisoning ?, trinitrotoluene poisoning ?*
  3. *Therapy*
     Alkalis, sulfonamides, arsenicals

able to classify this as a primary nutritional inadequacy. Practically, however, in view of the frequency with which disease may interfere with adequate food intake and because of the significance of this classification for preventive therapy, its inclusion as a conditioning factor is warranted. Gastrointestinal and neuropsychiatric disorders, fever, food allergy, and the nausea of pregnancy are noted for their interference with food intake, and the literature is replete with references to deficiency diseases developing under these conditions.

In hospitals a meal placed at the patient's bedside is often considered, on the record at least, as eaten, while actually the patient may have consumed little or none of it. Although this may occur under many conditions, it is particularly likely to occur in elderly patients whose hospitalization is more custodial than therapeutic, who may be confused, and whose dentures may be in the property room. Within one week 5 such patients with gross deficiency disease have been admitted to my service from "custodial" institutions, and an illustrative case was reported[16] of classic scurvy, pellagra, and riboflavin deficiency in a person transferred from a custodial institution where she had been a patient for five years.

Alcohol, though it also produces deficiency disease by other means,[12] may prevent an adequate food intake. It does this by replacing other food and by causing nausea and vomiting through its irritant action on the gastric mucosa. This may result in a thiamine deficiency causing anorexia, which in turn results in deficient intake of other nutrients. In this respect thiamine deficiency is frequently the underlying cause of other deficiencies. In some individuals the anorexia caused by lack of thiamine is a protective mechanism guarding against a high caloric intake.

Therapeutic measures often produce deficiency diseases by needlessly restricting the ingestion of certain essential nutritional factors. For example, diets prescribed for patients having allergy, peptic ulcers, biliary disease, nephritis, hypertension, colitis, diabetes, or obesity are often deficient in one or more of the essential nutrients. Such diets may occasionally produce more serious disease than the original condition for which the diet was prescribed. Especially harmful are certain unrational reducing diets. Fortunately their low caloric content gives some measure of protection for short periods of time, but, if persisted in, serious damage may occur. The physician should discourage such unbalanced diets.

Increased Requirements

Strictly speaking, malnutrition caused by failure to meet increased bodily requirements need not be considered as conditioned, since it is inadequate ingestion of food that is alone responsible. Practically, however, when the metabolic requirement is increased beyond the usual or average range, it is warranted to consider this as a conditioning factor. Fever increases the basal metabolism by 7.2 per cent for each Fahrenheit degree, while strenuous physical exertion may increase it to as much as fifteen times the basal level. The requirement of many nutritive essentials parallels total metabolism whether the change in total metabolism is brought about by physical exertion, disease, environment or drugs. This subject has been recently reviewed by Ershoff.[5]

The occurrence of deficiency diseases conditioned by fever, hyperthyroidism, pregnancy, and lactation is well known. Less well recognized are the effects of abnormal physical activity and unusual environmental factors. Johnson and his collaborators[10] have demonstrated an increased requirement of the B vitamins conditioned by moderately strenuous physical activity common to farmers, soldiers, and other workers. In a group of men subjected to physical labor equivalent to an output of 4000 to 5000 calories, definite deterioration in physical fitness occurred well within one week of starting labor with a diet deficient in the vitamin B complex. Such deterioration could be prevented or cured by the entire B complex containing only 0.6 mg. of thiamine daily but not by 2.0 mg. of thiamine hydrochloride alone. The applicability of these findings to workers in industry, to men in the armed forces, and to patients having delirium or a psychosis with pronounced increase in psychomotor activity is obvious.

Sunlight has been recognized as a precipitating agent in pellagra since Gheradini in 1792 produced pellagrous skin lesions on various parts of the body by exposure to the sun. In fact this disease is known among the peasants in Italy as *mal del sole*. Since the recognition of pellagra in this country, many clinicians have called attention to the possible relationship between exposure to sunlight and the development of the skin lesions. Others have confirmed Gheradini's experiments and in addition have shown that the same exposure in normal subjects leads only to the development of a healthy tan. Furthermore, other trauma, such as radiant energy, dirt, filth, or chemical trauma, is believed also to condition niacin-deficient persons to the development of skin lesions. Sunlight not only conditions these persons to skin lesions but is thought by some to play a role in conditioning riboflavin-deficient persons to corneal vascularity. Mechanical irritation has been shown to determine the localization of epithelial metaplasia in vitamin A deficiency, while ill-fitting dentures and edentulousness which causes caving in of the angles of the mouth may condition the lips to cheilosis.

By increasing total metabolism, various therapies may produce a conditioned deficiency disease. Drugs such as dinitrophenol, thyroxin, and thyroid, and fever therapy, act by increasing metabolism, while parenteral administration of dextrose, insulin shock therapy, and high carbohydrate diets act by increasing the requirement for coenzymes without an increase in total metabolism. Many investigators believe that long-continued parenteral administration of dextrose without parallel administration of water-soluble vitamins is dangerous to patients, particularly those in a borderline state of nutrition. The oxidation and decarboxylation of pyruvic acid, one of the intermediate products of carbohydrate metabolism, requires an enzyme-coenzyme system consisting of a specific protein enzyme (carboxylase), a cocarboxylase (thiamine-pyrophosphate), and magnesium. Other essential components in the mechanism of carbohydrate oxidation include flavoprotein, the dietary precursor of which is riboflavin, coenzymes I and II, the dietary precursor of which is niacin amide, adenosine triphosphate, and the iron-containing cytochrome system.[8] Bollman[2] has demonstrated that rats partially depleted of their stores of B vitamins and subsequently maintained with dextrose had a longer survival time if thiamine also was administered. No appreciable further effect was noted when the other B vitamins were supplied. Apparently the period of depletion had affected the body stores of thiamine more than it had the other factors of the B complex. The precipitation of deficiency diseases in man by dextrose infusions is well known. The "water-logging" after the parenteral administration of dextrose and saline solution is often a manifestation of deficiency. The preventive practice of simultaneously administering thiamine, riboflavin, niacin amide, and ascorbic acid along with each dextrose infusion is based on sound theoretical and practical considerations.

Excessive consumption of carbohydrate acts in the same way as parenteral administration of dextrose and there is much evidence in the literature that this is a common method of inducing deficiency diseases.

Interference with Absorption

As our knowledge of deficiency diseases increases it becomes more and more evident that disturbances of absorption from the intestinal tract play an important role in the production of deficiency disease. Absorption may be impaired because of anatomic, chemical, or physiologic changes. These changes are mediated by reduced absorbing surfaces, altered secretions, and hypermotility, and are further modified by various alkalis, adsorbents, and lubricants introduced by mouth.

In the diarrheal diseases hypermotility plays the most important role, since the rapid passage of food through the intestinal tract does not allow sufficient time for digestion, solution, and absorption of the essential factors. In the more chronic diarrheal states, as chronic ulcerative colitis, reduction of absorbing surfaces may be equally important. The clinical importance of diarrhea in producing deficiency disease is evidenced by the many recent reports of pellagra, beriberi, scurvy, riboflavin deficiency, vitamin A deficiency, protein deficiency edema, and hypocalcemia induced by this conditioning factor.

Achlorhydria may impair the absorption of ascorbic acid and of thiamine. Because of its particular prevalence in elderly people, achlorhydria always should be suspected in unexplained malnutrition, and malnutrition should be looked for in every patient having achlorhydria.

The role of bile salts in the absorption of the fat-soluble vitamins, particularly K, is so well known that it need only be mentioned.

The role of vitamin deficiencies themselves in acting as a conditioning factor by impairing absorption is beginning to be recognized. The intestinal absorption of galactose and probably other sugars is impaired in experimental B-complex deficiencies in the rat and in the dog. Lepore and Golden[23] were the first to report X-ray evidence of a characteristic small-intestine lesion in some cases of deficiency disease. It is believed that the impaired absorption is caused by disturbances in motility.

Therapy may play an important role in interfering with absorption. Gastrointestinal surgery, particularly resection and short-circuiting operations, has long been known to produce macrocytic anemia similar to pernicious anemia, and there are many case reports to indict it as a factor in the production of other deficiency syndromes. Ingestion of liquid petrolatum daily or almost daily is a common practice among many people who are well except for constipation of varying degrees. That such an agent interferes with the absorption of carotene is well known.

INTERFERENCE WITH UTILIZATION

This factor is extremely complex and difficult to verify by direct experimentation. Evidence of interference with utilization is largely circumstantial. In the presence of an adequate intake it is necessary to rule out malabsorption, increased destruction in the bowel, excessive excretion, and abnormal requirement before concluding that utilization is defective. It is known, for instance, that the body must convert carotene to vitamin A, phosphorylate thiamine to cocarboxylase, and convert nicotinic acid as its amide to coenzymes I and II, and that riboflavin is essential to more enzyme systems than any other of the known vitamins. Some of these changes may occur in tissue cells in general, but the evidence at this time indicates that the liver is the main organ in which these processes take place. Be that as it may, it is in hepatic disturbances that malutilization is most frequently encountered. In the presence of liver dysfunction these disturbances may be due not only to failure of conversion but to inability of the liver to store a nutrient. The body is then dependent on the day-to-day intake. This intake naturally varies, with the result that an excess today cannot be stored for a deficit almost certain to occur on some future day. A tissue deficiency in vitamin A attributable to impaired conversion of carotene to vitamin A has been reported in liver cirrhosis, diabetes mellitus, obstructive jaundice, and hypothyroidism. The low plasma levels of vitamin A observed at times in patients having gastrointestinal cancer have been explained as a failure to utilize due to hepatic dysfunction. The high frequency of nutritional diseases in alcohol addicts is well known. Hepatic dysfunction undoubtedly plays a role in these cases.

Therapy also may interfere with the utilization of vitamins. Deficiency disease produced by sulfonamide compounds has been attributed mainly to sterilization of the intestinal tract and inhibition of intestinal synthesis of certain factors.

Increased Excretion

The role of increased excretion of vitamins in the production of malnutrition has received little attention, although the production of hypoproteinemia by albuminuria, and salt depletion either by excessive sweating or by polyuria, are well-known phenomena. Cowgill[3] has shown that vitamin B_1 deficiency symptoms appear earlier in dogs maintained with a forced water intake than in dogs that were permitted to drink water ad libitum. He attributed this to increased excretion of vitamin B_1. The possibility of "washing out" the water-soluble vitamins must therefore be considered in uncontrolled diabetes mellitus and diabetes insipidus. The loss of vitamins by lactation may be a precipitating factor in deficiency diseases. Severe gestational polyneuropathy has been observed in patients who showed only minor symptoms during pregnancy but rapidly developed the serious condition during the second week postpartum. The drain of lactation was apparently the last straw in the pathogenesis of this severe thiamine deficiency.

The determination of vitamins in the sweat is technically difficult. The practical significance of vitamin depletion by excessive perspiration is probably minimal.

By increasing excretion, therapy may contribute to the production of deficiency disease. The forcing of fluids, especially over long periods of time as in certain urinary tract infections, and the loss of fluids by diuresis, as in anasarca, may be the last straw required to produce a deficiency.

INCREASED DESTRUCTION

Increased destruction of vitamins may occur in the gastrointestinal tract prior to absorption or in the tissues following absorption. The conditioning factors thought to cause increased destruction of vitamins in human beings are listed in Table 7. This list does not include either induced thiamine deficiency in animals caused by enzymatic destruction of thiamine by raw carp or of biotin deficiency in man induced by egg white injury, as neither has been shown to occur spontaneously in man, although neither is beyond theoretical possibility.

The susceptibility of ascorbic acid and thiamine to destruction in alkaline environment has led to some investigation of the role played by achlorhydria and alkaline therapy. Alt, Chinn, and Farmer[1] have shown a 65 per cent destruction of ascorbic acid in three hours at a *p*H of 7.95, representing achlorhydric gastric juice, and obtained results in patients with achlorhydria suggesting decreased assimilation of ascorbic acid. Wright and Ludden[32] have also observed signs of vitamin C deficiency in persons with achlorhydria in spite of a liberal ascorbic acid intake. They were also able to demonstrate lack of absorption in these subjects after an oral test dose.

Melnick, Robinson, and Field[6, 25] have shown that thiamine is stable in gastric juice over a *p*H range of 1.5 to 8.0 during sixteen hours of incubation. In the presence of added antacids the thiamine was completely destroyed, and in the presence of bile or pancreatic juices 50 to 90 per cent was destroyed. The same investigators noted subnormal urinary excretion of a test dose of thiamine in subjects who were given alkalis. Other work also indicates that achlorhydria may interfere with the absorption of thiamine.

NUTRIENT RESERVES

In the first part of this chapter a nutritional inadequacy was traced to either a primary (dietary) inadequacy or to a secondary (conditioned) inadequacy. The mere presence of a nutritional inadequacy, however, does not necessarily indicate either malnutrition or deficiency disease, for the human body has interposed an important safety factor between the occurrence of a nutritional inadequacy and the development of deficiency disease. This safety factor is the nutrient reserves upon which the tissues may draw during temporary lapses in the supply of nutrients. These reserves may be very large, as in the case of vitamin A, when several months' normal supply may be stored in the liver of a previously well-fed adult. The reserves may also be relatively small, as with thiamine, when several days of total deprivation are sufficient to deplete the nutrient reserve. The function of these reserves is to maintain the tissues with a relatively constant supply of nutrients. If the supply from the gut is temporarily inadequate the reserves release nutrients to the tissues via the blood. If the supply from the gut is temporarily greater than the tissue requirements, nutrient reserves are filled first, and if the supply is still in excess the balance piles up temporarily in the blood, to be eliminated in most instances in the urine. This accounts for the large urinary excretion of nutrients following test doses if the nutrient reserves are filled, and the low urinary excretion of test doses if the reserves are low or depleted. According to this concept the blood levels of vitamins represent the nutrients in transport either from the nutrient reserves to the tissues or from the gut to the tissues or to the nutrient reserves. When transport is active, as after recent ingestion, or when tissue levels are low and tissue stores are releasing nutrients, blood levels of nutrients tend to be normal or high. When tissue levels are normal and no nutrients are entering through the gut, the blood levels of the nutrients tend to be low even if the nutrient reserves are normal. If tissue levels are low, blood levels tend to remain normal if the tissue reserves are adequate because of transport from nutrient reserves to the tissues. It is the interaction of all these factors that renders interpretation of blood levels of nutrients difficult. (See Chapters 4 and 6.)

THE DEVELOPMENT OF DEFICIENCY DISEASES FOLLOWING EXHAUSTION OF NUTRIENT RESERVES

Tissue Depletion

Up to the point of depletion of the tissue levels of nutrients to a critical degree, a nutritional deficiency disease literally does not exist. Just as the water reservoir of a great city continues to supply the inhabitants during a dry season of usual length, so the nutrient reserves of the body continue to supply essential nutrients to the tissues for reasonable periods of time. If, however, the sources of water supply over a protracted period are less than the needs of the people the reservoir will eventually become exhausted and the city will become dependent on the day-to-day rainfall. Similarly, if the nutrient supply continues to be less than the tissue requirements, the reserves will eventually be depleted, so that the tissues will be dependent on the daily food supply. Tissue depletion may occur rapidly or slowly, depending upon various factors: (1) the degree of nutritional inadequacy, (2) the amount of nutrient reserves, and (3) the requirement of the body for essential nutrients. The interplay of the first two factors will be discussed later (page 34) in the section on acute and chronic lesions of nutritional deficiency diseases.

Dietary "Requirements" and "Allowances"

Estimation of the requirements of the body for its various essential nutrients has provoked much controversy and difference of opinion, perhaps more than any other phase of nutrition. The individual requirements will be given in the chapters dealing with each essential nutrient, but the different philosophies by which "requirements" and "allowances" have been arrived at will be presented here briefly.

A *dietary requirement* may be defined as the amount of a specific nutrient which is needed, *without a safety factor,* in order to attain a specified degree of health under definite conditions of age, weight, activity, food intake, physiologic status, and pathologic condition. Difficulties other than technical in arriving at this requirement arise from the definition of "health" and from the fact that all physiologic attributes are characterized by variation. Health has notoriously defied definition. Some investigators accept health as the absence of readily observable lesions of disease. This usually means the absence of lesions not frequently found in or not characteristic of the population group with which they are familiar. For example, a decreased density of the bones to X-rays is so common in China that it is often considered a normal variant. The same degree of demineralization in this country would be labeled definitely as osteomalacia—a disease. Acceptance of this definition of health also means skepticism concerning the possible benefits to be derived from nutrition beyond the prevention of classic florid deficiency disease, or belief that the benefits are of such minor importance in the total health picture that they can be disregarded. Other investigators consider health to have positive attributes of optimum growth, development, efficiency, and resistance to disease. (See Chapter 30.)

The second factor complicating the setting of a requirement is the normal variability of all physiologic attributes, even when measured under similar conditions of age, sex, activity, etc. Just as the metabolism varies under basal conditions so does the requirement for nutrients vary under similar conditions. Pett[26] used the calcium balance to illustrate this variability. Of 97 persons studied, calcium balance was achieved at the following levels: less than 0.35 gm.—22; between 0.35 and 0.55 gm.—54; between 0.55 and 0.70 gm.—18; and over 0.70 gm.—3. The average and the mode for this group ranged between 0.40 and 0.45 gm. of calcium daily. Examples of this variability can be given for most of the other nutrients. In addition to the normal physiologic variability the body can apparently adapt itself under certain conditions to smaller supplies.

In an entirely different category than "dietary requirement" are the Dietary Allowances of the National Research Council (Appendix, Table A) which, in spite of repeated disclaimers, have been interpreted as "requirements." These allowances were derived by taking the average requirement according to age, sex, caloric intake, and physiologic attributes so that persons with higher than average requirements would be included within the "allowances." Thus the Daily Allowances are neither "minimum," "average," nor "optimal" requirements but "allowances" of various nutrients that will provide to groups of people levels of nutrients now considered satisfactory for all normal persons included in that group.

BIOCHEMICAL LESIONS

When tissue depletion has reached a critical level, biochemical "lesions" result. These lesions are not too well known to the clinician though the biochemist is beginning to be familiar with changes in the enzyme systems induced by tissue depletion of several of the nutrients. Possibly the best known of these biochemical lesions is the accumulation of pyruvic acid in the blood and in the tissues as a result of thiamine depletion, and the appearance of certain fluorescent substances in the urine in consequence of niacin depletion. (See Chapter 4.)

FUNCTIONAL CHANGES

Following biochemical lesions various functional changes occur. These functional changes are manifested clinically by symptoms usually placed in the neurasthenic syndrome. They include such common complaints as excessive fatigability, disturbances in sleep, inability to concentrate, "gas," heart consciousness, and various queer bodily sensations. Although these symptoms are definitely nonspecific in that they may be caused by very many factors other than nutrition, their occurrence as a manifestation of tissue depletion of certain nutrients is undoubted.

Other more objective functional alterations can be demonstrated by special technics. Among these are inability to see in dim light, related to vitamin A depletion; bradycardia and certain electrocardiographic changes, noted in thiamine deficiency; "puddling" and other changes in the small-intestine X-ray pattern, noted in vitamin B-complex deficient subjects. Changes in work performance demonstrable by several varieties of tests occur particularly in B-complex depletion.

ANATOMIC LESIONS

Following functional changes, anatomic lesions become manifest. At first they are sub-gross, that is, microscopic in nature. It is axiomatic that gross lesions must be preceded by sub-gross lesions, hence it is entirely reasonable to investigate tissues readily available for examination by the biomicroscope, such as the conjunctiva, the cornea, the tongue, and the gums, since those tissues are known to develop gross lesions as a result of tissue depletion. The conjunctivae develop Bitot's spots in advanced Vitamin A deficiency; the cornea may develop vascularity in riboflavin deficiency; the tongue shows glossitis in several deficiency diseases, and the gums become hemorrhagic in scurvy. Kruse has described in each of these tissues sub-gross lesions which he attributes to specific deficiencies.[18, 20, 29] Most workers, however, do not subscribe to the specificity of these lesions and the biomicroscope has not become a widely used research tool in clinical nutrition as its practical utility has not been accepted.

Following sub-gross lesions, gross manifestations become evident. These are described collectively in the chapter on clinical signs (Chapter 3) and in each of the chapters on the specific nutrients. It is only the more advanced of these gross lesions that are generally recognized today, so that most diagnosed malnutrition is that which has advanced to the late stages.

THE CONCEPT OF ACUTE AND CHRONIC DEFICIENCY DISEASES*

The terms acute, subacute, or chronic are used to designate the speed or velocity of change in the pathologic lesion. Acute lesions are rapid in development, rapid in progress, and if adequately treated, rapid in recession. Chronic lesions are slow in development, slow in progress, and even with adequate therapy, slow in recession. Some may be irreversible. Subacute lesions fall between these two extremes. The velocity of the lesion is determined by the rate of change in the tissue concentration of the essential nutrient. A sudden change from adequate to grossly inadequate intake of an essential nutrient with limited reserves will result in a rapid change in tissue concentration and will initiate rapid changes in biochemical composition, in function, and in morphology. If these changes are rapid and severe enough, death will ensue with little or no morphologic change. An example is the pigeon placed on a diet markedly deficient in thiamine. It will develop head retraction and, if untreated, will die rapidly, but morphologic changes will not be found as a rule. The same pigeon, if given a small dose of thiamine, will be able to fly in one hour.

Chronic lesions represent pathologic changes initiated by slow changes in tissue concentration of an essential nutrient. Although the level may be the same as in the acute variety, the time required to bring it to that level determines, in many instances, the pathologic response. When the change is slow, the anatomic response is slow in onset, slow in development, and slow in recession. To use the previous illustration, if the pigeon is given a diet only partially deficient it does not develop head retraction but after a time, a much longer time, develops polyneuropathy. If treated with thiamine this pigeon does not recover within the hour, as does the acutely deficient pigeon, but days or weeks of treatment are required.

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* This concept has been developed by Kruse and for a fuller exposition the reader is referred to his original articles.[21, 22]

Not to be confused with the terms acute and chronic are the terms mild and severe. An acute lesion is not necessarily severe—it can equally well be moderate or mild. A chronic lesion is not necessarily mild—it can be moderate or severe. The terms indicate intensity of the pathologic response. For maximum intensity of an acute lesion—a severe acute lesion—there must be a sudden or rapid change in tissue concentration from normal or near normal to very low. For milder intensity of an acute lesion—a mild acute lesion—there must be a rapid change in tissue concentration from normal or near normal to an intermediate level. Similarly, for maximum intensity of a chronic lesion—a severe chronic lesion—there must be a slow or gradual change in tissue concentration from normal or near normal to very low. For milder intensity of a chronic lesion there must be a slow or gradual change in tissue concentration to intermediate levels. Everything else being equal, mild lesions respond more readily than severe lesions. On the other hand, the velocity controls speed of recession more than the intensity, for a mild chronic lesion responds more slowly than a severe acute lesion.

Thus far the velocity and intensity of the lesions have been presented in their simplest form—that is, as if they arose in normal tissue and as if with therapy their cure were complete. In practice, events are more complex. In the acute form there are several possible developments. First, especially if the lesions are severe, the patient may die. Second, especially if they are mild, the patient becomes inactive and develops a poor appetite. Both of these latter developments are protective mechanisms decreasing the requirement, which in effect reduces the velocity of the tissue deficiency so that the lesion is likely to become chronic. As a third eventuality the appetite may improve, a better diet may be taken, or the patient may receive inadequate therapy; this results in incomplete cure and a chronic lesion.

The chronic lesions may progress more or less uneventfully throughout life. More often than not acute episodes are superimposed on the chronic base—as the pellagrins who each spring develop acute signs on the old chronic base. In these subjects relief of the acute changes is often erroneously thought to constitute a cure.

The pathologic lesions of malnutrition have, in addition to velocity and intensity, the factor of duration. Thus a mild or severe chronic lesion may be early or late. It is much more difficult to cure a late mild chronic than an early severe chronic lesion. The first may have advanced beyond reversibility; the latter may still be reversible. For example, a polyneuropathy of one month's duration manifest clinically by bilateral wrist and ankle drop, absence of ankle and knee jerks, and characteristic sensory changes, responds better to therapy than a polyneuropathy of one year's duration manifest clinically only by absence of ankle jerks and characteristic sensory changes. The lesions of long duration may never respond; those of shorter duration will almost always do so.

The importance of duration is restricted largely to lesions of chronic velocity. Acute lesions are nearly always early—for by the time they become late the velocity has so slowed that they are chronic.

The concept of acute and chronic velocity and of mild and severe intensity is not just a theoretical fancy. It can be observed both in experimental animals and in man.

BIBLIOGRAPHY

1. Alt, H. L., Chinn, H., and Farmer, C. J. The blood plasma ascorbic acid in patients with achlorhydria (pernicious and iron deficiency anemia). *Am. J. M. Sc.* 197:299, 1939.
2. Bollman, J. L. Dextrose administration and vitamins B. *Proc. Soc. Exper. Biol. & Med.* 50:18, 1942.
3. Cowgill, G. R. Vitamin B Requirement of Man. New Haven, Yale, 1934.
4. Editorial: "Inadequate diets and nutritional deficiencies in the United States." *J.A.M.A.* 124:1137, 1944.
5. Ershoff, B. H. Conditioning factors in nutritional disease. *Physiol. Rev.* 28:107, 1948.
6. Field, H., Jr., Robinson, W. D., and Melnick, D. Destruction of thiamine by unacidified bile and pancreatic juice: a possible explanation of the cord changes in pernicious anemia. *J. Clin. Investigation* 19:791, 1940.
7. "Gallup poll tests wartime eating habits" (News from the Field). *Am. J. Pub. Health* 33:470, 1943.
8. Goodhart, R. S., and Bueding, E. Carbohydrate metabolism in practice of medicine. *M. Clin. North America* 27:315, 1943.
9. Jellinek, E. M. Recent Trends in Alcoholism and in Alcohol Consumption. New Haven, Hillhouse Press, 1947.
10. Johnson, R. E., Darling, R. C., Forbes, W. H., Brouha, L., Egana, E., and Graybiel, A. The effects of a diet deficient in part of the vitamin B complex on men doing manual labor. *J. Nutrition* 24:585, 1942.

11. Jolliffe, N. A clinical evaluation of the adequacy of vitamin B_1 in the American diet. *Internat. Clin.* 4:47, 1938.

12. Jolliffe, N. The influence of alcohol on the adequacy of the B vitamins in the American diet. *Quart. J. Stud. on Alcohol* 1:74, 1940.

13. Jolliffe, N. "Nutrition and the deficiency diseases" in Preventive Medi*cine in Modern Practice.* New York, Hoeber, 1942.

14. Jolliffe, N. Conditioned malnutrition. *J.A.M.A.* 122:209, 1943.

15. Jolliffe, N. The preventive and therapeutic use of vitamins. *J.A.M.A.* 129:613, 1945.

16. Jolliffe, N., Fein, H. D., and Rosenblum, L. A. Riboflavin deficiency in man. *New England J. Med.* 221:921, 1939.

17. Jolliffe, N., McLester, J. S., and Sherman, H. C. Prevalence of malnutrition. *J.A.M.A.* 118:944, 1942.

18. Kruse, H. D. Medical evaluation of the nutritional status: IV. The ocular manifestations of avitaminosis A, with especial consideration of the detection of early changes by biomicroscopy. *Pub. Health Rep.* 56:1301, 1941; *Milbank Mem. Fund Quart.* 19:207, 1941.

19. Kruse, H. D. The gingival manifestations of avitaminosis C, with especial consideration of the early changes by biomicroscopy. *Milbank Mem. Fund Quart.* 20:290, 1942.

20. Kruse, H. D. The lingual manifestations of aniacinosis, with especial consideration of the detection of early changes by biomicroscopy. *Milbank Mem. Fund Quart.* 20:262, 1942.

21. Kruse, H. D. A concept of malnutrition. *Milbank Mem. Fund. Quart.* 20:245, 1942.

22. Kruse, H. D. The place of nutrition in the relationship between environment and health. *Milbank Mem. Fund Quart.* 26:41, 1948.

23. Lepore, M. J., and Golden, R. A syndrome due to deficiency of vitamin B complex. *J.A.M.A.* 117:918, 1941.

24. Lockhart, E. E., Harris, R. S., Tapin, E. W., Lockhart, H. S., Nutter, M. K., Tiffany, V., and Nagel, A. H. Study of the nutritional quality of dietaries by chemical analysis. *J. Am. Dietet. A.* 20:742, 1944.

25. Melnick, D., Robinson, W. D., and Field, H., Jr. Fate of thiamine in the digestive secretions. *J. Biol. Chem.* 138:49, 1941.

26. Pett, L. B. Errors in applying nutrient allowances to dietary servings or food policies. *Canadian J. Pub. Health* 36:69, 1945.

27. Phipard, E. F., and Adelson, S. F. Family food consumption in the United States, spring 1942. *Misc. Pub.* 550, U. S. Dept. Agric., 1944.

28. Report of the Committee on Diagnosis and Pathology of Nutritional Deficiencies, Food and Nutrition Board: "Inadequate diets and nutritional deficiencies in the United States. Their prevalence and significance." *Bulletin of the National Research Council,* No. 109, 1943.

29. Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M., and Kruse, H. D. The ocular manifestations of ariboflavinosis. *J.A.M.A.* 114:2437, 1940.

30. Wilder, R. M. Misinterpretations and misuse of the Recommended Dietary Allowances. *Science* 101:285, 1945.

31. Williams, R. D., and Wilder, R. M. The prevalence of malnutrition in the American population: A review of the evidence. National Research Council Report, 1941.

32. Wright, I. S., and Ludden, J. B. Treatment with vitamin C (cevitamic acid—ascorbic acid); Method for compensating for the factor of error due to renal retention of vitamin C found in all previous saturation and blood tests. *M. Clin. North America* 24:743, 1940.

Chapter 2

THE DIETARY AND MEDICAL HISTORY

Norman Jolliffe

THE complete diagnosis of deficiency diseases, which includes an assessment of etiology, depends upon a critical evaluation of the clinical signs after they have been correlated with the dietary and medical history and with findings from the chemical, hematologic, X-ray, electrocardiographic, and other special laboratories. Perhaps in no other branch of diagnosis is this evaluation fraught with more pitfalls than in the diagnosis of a specific nutritional deficiency. The aids now used in the diagnosis of malnutrition may be compared in reliability to those used in the diagnosis of pulmonary tuberculosis before the X-ray, typhoid fever before bacteriologic and agglutination tests, and syphilis before the serologic tests. Laboratory and other special tests are being developed and applied in clinical investigations, but except in isolated instances their chief value at this time is in group survey studies and as research tools not yet ready for routine use in any one individual patient. For those reasons the dietary and medical history and the clinical examination will be discussed in greater detail than may be necessary in another decade.

DIETARY HISTORY

The purpose of the dietary history is to detect unsatisfactory dietary patterns which may be the cause of deficiency disease. If a deficiency disease already exists, a clue to its etiology may be found; if a deficiency

TABLE 8. CHECK LIST FOR EVALUATION OF DIETARY PATTERN

Food group	*Satisfactory daily amounts*	*Primary Purpose*	*Satisfactory daily amounts used weekly*		
			0–2 Poor	3–5 Indeterminate	6–7 Satisfactory
1. Citrus fruit or juice; or twice the amount of tomatoes or juice	Lactation: 2 servings Others: 1 serving	Vitamin C			
2. Milk: whole (fresh or canned), skimmed, dried, or buttermilk; Vitamin D milk for children	Children: 2, 3, or 4 cups daily according to age Adolescent and postadolescent boys & lactation: 6 cups Pregnancy: 4 cups All others: 2 cups	Calcium, riboflavin, protein, vitamin D for children			
3. Lean meat, fish, fowl, or 2 eggs	100 Gm. portion—1 serving	Protein, thiamine, niacin, iron			
4. Salad (raw fruit or vegetable)	100 Gm. portion—1 serving	Hemicellulose			
5. Cooked fruit or vegetables	100 Gm. portion—2 servings	Hemicellulose, iron			
One serving of either Group 4 or 5 should be leafy green or yellow		Vitamin A			
6. Enriched or whole grain bread and cereals (1 serving of cereal equals 2 slices of bread)	Sedentary person: 4–6 slices Moderate activity: 6–8 slices Active: 8-10 slices	Thiamine, niacin, iron, calories			
7. Butter or fortified margarine	3 level tablespoonfuls	Fat			

8. Unenriched cereals and bread; pastries; cake, jellies, candy; sugar; sweetened carbonated and alcoholic beverages	In moderation (1 or 2 servings daily)	Calories	Excess	Moderation

Supplementation: Yes.......... No........
If yes, what:..............................
....
....
For how long:..............................
....

Summary of Diet	*Poor*	*Indeterminate*	*Satisfactory*
pattern			
Calories			
Protein			
Calcium			
Iron			
Vitamin A			
D			
C			
Thiamine			
Riboflavin			
Niacin			

disease is not present, the correction of an unsatisfactory pattern is good preventive medicine.

The dietary history may be obtained qualitatively or quantitatively, depending upon its purpose.

QUALITATIVE DIETARY PATTERN RECORD

A rapid evaluation of the dietary pattern in qualitative terms is all that is usually necessary in office, hospital, or clinic practice. Most physicians do not have the time, information, inclination, or personnel necessary for the quantitative evaluation of a diet in terms of grams, milligrams, or units of each of the nutrients. The author[1] has found a summary check list valuable in the qualitative estimation of dietary patterns. Completion of this check list (Table 8) requires no more than five minutes. If the dietary pattern is satisfactory and subsequent examinations disclose no evidence of disease or of malnutrition, a quantitative evaluation would serve no practical purpose. In many instances an unsatisfactory dietary pattern correlated with deficiency disease does not require quantitative evaluation, except for research purposes. The qualitative information is usually so clear-cut that additional data would be superfluous.

Results of the use of this check list, compared with results of dietary analyses by conventional quantitative methods, show that if the dietary in all food groups is checked as satisfactory, the chances are high that the quantitative evaluation of each nutrient would approximate the National Research Council's dietary allowances. On the other hand, if the dietary is checked as poor in all food groups, the chances are that most nutrients would be quantitatively evaluated at much less than those allowances. Thus both poor and satisfactory dietary patterns, except for research purposes, seldom require quantitative determination.

But what about dietary patterns neither completely satisfactory nor completely poor—diets with check marks scattering among poor, indeterminate, and satisfactory? In general, a check mark in the "poor" column usually means that the patient is consuming much less than the National Research Council's daily allowance of the indicated nutrient. A check mark in the "satisfactory" column usually means that the patient is consuming approximately the National Research Council's daily allowance of the indicated nutrient, and the diet may be considered satisfactory in the indicated nutrient unless the patient consumes excess amounts of items in group 8.

These rules are, of course, only rough guides and many exceptions can be found, for no single food group is absolutely essential. In Table 9 the most common substitutions for the various food groups are shown. Still more detailed are the food charts (Appendix Table B) which give the nutrient contributions of average servings of many commonly used foods.

Quantitative Estimation of the Diet

The quantitative estimation of the patient's food consumption at home, in terms of specific nutrients, is often desirable in order to correlate the nutrient intake with the laboratory or clinical findings. It is also important in the development of public health nutrition programs, teaching, study of food habits, and appraisal of the dietaries of groups of people. It is desirable also in certain instances in practical nutrition when the qualitative dietary pattern and the laboratory or clinical findings are not consistent. The results, however, should not be regarded by the physician as having the accuracy of many laboratory reports, for these data do not lend themselves to precise quantitative estimation. Even if the patient's memory is accurate, his interpretation of the size of portions reasonably accurate, and his desire to translate "what he should have eaten" into "what he ate" held in check, the variability in the nutritive composition

Table 9. COMMON SUBSTITUTIONS FOR FOOD GROUPS LISTED IN TABLE 8

In absence of:	*Nutrient likely to be unsatisfactory*	*Deficit can be met by increased consumption of:*
Group 1	Vitamin C	Groups 4 and 5; pharmaceutical preparations
Group 2	Calcium	Certain greens in Groups 4 and 5; cheddar cheese; hot breads made with self-rising flour; calcium-enriched breads in England; pharmaceutical preparations
	Riboflavin	Liver; brewer's yeast; pharmaceutical preparations
	Protein	Group 3; pharmaceutical preparations
	Vitamin D	Fish oils; pharmaceutical preparations
Group 3	Protein	Group 2; pharmaceutical preparations
	Thiamine and niacin	Liver; brewer's yeast; Group 6; pharmaceutical preparations
	Iron	Groups 5 and 6; pharmaceutical preparations
Group 4	Hemicellulose	Group 5; pharmaceutical preparations
Group 5	Hemicellulose	Group 4; pharmaceutical preparations
	Iron	Groups 3 and 6; liver; pharmaceutical preparations
	Vitamin A	Liver; fish oils; pharmaceutical preparations
Group 6	Thiamine and niacin	Groups 3, 4 and 5; liver; brewer's yeast; pharmaceutical preparations
	Iron	Groups 3 and 5; pharmaceutical preparations
	Calories	All other foods
Group 7	Fat	The "invisible" fat in meat, eggs, milk, cream, and whole cheese

of the same food under different soils and seasons and various means of transportation, storage, cooking, and serving is so great that the quantitative estimation of nutrients cannot be accepted with the same confidence as can many well-established laboratory reports. All quantitative reports of nutrients contained in home dietaries should be considered with these limitations in mind.

There are various methods of obtaining a dietary record. The first and simplest is to obtain from the patient a typical menu of the foods used at regular meals and between meals. The previous day or two-day menu is about as long a period as most people can remember what they have eaten.

A second method is to obtain a food intake record or dietary over a period of a week. This record can be compared with a food purchase record, especially if family dietaries are being estimated. From these data a list of foods actually eaten by the patient can be tabulated. Quantitative computation of this list can then be made by comparison with Food Value Tables (Appendix Table B) and reported to the doctor on a summary form such as that recommended by Turner[2] (Table 10).

MEDICAL HISTORY

The medical history is extremely important in the diagnosis of deficiency disease. As noted in the chapter on pathogenesis of deficiency disease, past or present illness may contribute to malnutrition in that decreased intake, impaired digestion or absorption or utilization, increased requirements, or accelerated excretion may be as potent a factor as improper dietary in producing nutritional failure. As a matter of fact, among hospitalized patients these conditioning factors probably play a role in most of those patients having malnutrition. In this way peptic ulcer, diarrheal disease, disturbances of the liver or gallbladder, diabetes mellitus, hyperthyroidism, pregnancy, and lactation, are a few of the conditions which can be indicted etiologically when deficiency disease is being investigated. Therapy, too, as in the treatment of allergies, obesity, diabetes mellitus, peptic ulcer, and gallbladder disease, may contribute to deficiency disease by dietary limitations.

In the medical history, symptoms must be carefully evaluated. Among the complaints that may be significant are easy fatigability, somnolence, anorexia, photophobia, night blindness, burning of the eyes, lacrimation, burning of the tongue and mouth when tart foods are eaten, easy bleeding of the gums, palpitation, heart consciousness, dyspnea, frequent eructations of gas, diarrhea, hyperesthesia, paresthesias or anesthesias of the fingers or toes, and sore lips and angles of the mouth. These symptoms

TABLE 10. TRENDS OF PRESENT DIETARY INTAKE*

Name.................... Unit No.................. Date.....................

I. *Summary of usual daily food intake:*

Amount of:
- Milk
- Cheese
- Eggs
- Meat, fish, or fowl
- Vegetables
- Fruit

Amount of:
- Potato
- Bread
- Cereal
- Sweets
- Fats
- Other foods
- Beverages

II. *Evaluation:*

A. Approximate analysis
1. Calories.....................
   Carbohydrate.................
   Protein:
      Good quality................
      Poor quality................
   Fat..........................
2. Minerals:
   Calcium......................
   Phosphorus...................
   Iron.........................
3. Vitamins:
   Vitamin A....................
   Thiamine.....................
   Ascorbic acid................
   Vitamin D....................
   Riboflavin...................

B. Tentative standards
1. Calories.....................

   Protein:

2. Minerals:
   Calcium......................
   Phosphorus...................
   Iron.........................
3. Vitamins:
   Vitamin A....................
   Thiamine.....................
   Ascorbic acid................
   Vitamin D....................
   Riboflavin...................

III. *Pertinent information:*

How long has present diet been in use?
Any previous special diets? Kind? How long?
Vitamin preparations used?
Regularity of meals?
Distribution of food?
Where is food eaten?
Appetite?
Food dislikes?
Food idiosyncrasies?
Income?

IV. *Impression:*

Diet Recommendations

---

* Reprinted from Turner, D., Handbook of Diet Therapy, the University of Chicago Press, 1946, by permission of the author, the University of Chicago Press, and the American Dietetic Association.

TABLE 11. HISTORY FORM

NO.

NUTRITION CLINIC, DEPARTMENT OF HEALTH, CITY OF NEW YORK

Name Address Boro

Age
Birthdate
Sex
Color
Birth-place

Occupation
School Grade

Economic Status
Relief Marginal Adequate
Marital Status
S M W D

Referred by:
Reason:

No. Rooms
Monthly rent
Central heating Yes No
Bathroom in Apartment Yes No

Members of Family	Date Birth	Date Death	Birth-place	Occupation	Income	
					Gross	Net
Father						
Mother						
Siblings						
1.						
2.						
3						
4.						
5.						
6						
7.						
8.						
				Other Income		
				Total Income		

Others in Household *Relationship*

Known to Agencies *Address* *Reason*

Table 11. (*Continued*)

DATE

Previous Illnesses

Family History — Tuberculosis — Other

Developmental History — Walked at — Talked at — First tooth

Menstrual History — Normal — Abnormal — Age onset — Age menopause — No. pregnancies — No. miscarriages — No. children

Conditioning factors for present nutritional state

Gastroenteritis
Peptic ulcer
Diarrheal disease
Gallbladder disease
Liver disease
Congestive heart failure
Other heart disease
Food allergy
Operations

Alcoholism
Edentulism
Restricted diet
Mineral oil
Pregnancy
Lactation
Diabetes
Hypothyroidism
Hyperthyroidism

Anorexia
Rheumatic fever
Malignancy
Tuberculosis
Use of thyroid extract
Chronic indigestion
Scarlet fever
Measles
Pertussis

Present complaints

Fatigue: AM PM
Weakness

Weight: Loss
Gain

Sleep: Insomnia
Somnolence

Eyes:
- Burning
- Itching
- Photophobia
- Lacrimation
- Blurring of vision
- Night blindness

Lips and mouth:
- Sore lips
- Sore angles
- Sore tongue
- Bleeding gums
- Condition of teeth
- Edentulous
- Plates

Gastro-intestinal:
- Anorexia
- Gas
- Diarrhea
- Nausea
- Vomiting
- Heartburn
- Indigestion-pain
- Constipation

Cardio-Renal:
- Chest pain
- Palpitation
- Dyspnea
- Orthopnea
- Cough
- Nocturia
- Dysuria
- Edema

Skin:
- Dermatitis
- Location
- Onset

ENT:
- Diseased tonsils
- Frequent sore throats

Genito-urinary:
- Vaginitis
- Urethritis
- Perineal lesions

Allergy:
- Sensitivity to:
  - heat foods
  - cold
- Skin rashes
- Asthma
- Urticaria
- Hay fever
- Other

Mental State:
- General nervousness
- Emotional
- Apathetic
- Retarded school work

Neurological and Vasomotor:
- Headache
- Dizziness
- Tinnitus
- Migraine
- Vertigo
- Flushing
- Paresthesias of hands, feet, or tongue

Musculo-skeletal:
- Joint pains
- Muscle pains
- Muscle cramps

Other:

Previous Vitamin Medication____________________
Present Vitamin Medication____________________

Summary:

Signature____________________

must be weighed, and when all other causes have been ruled out, a nutritional origin may be suspected. The mother's story of a child's lack of appetite, lethargy, failure to gain weight and grow properly, irritability, or easy bruising may be a clue to illness of nutritional origin.

Table 11 shows the history form used in the Nutrition Clinic of the Department of Health of the City of New York, which the author has found valuable in recording both the history of disease and the complaints of the patient.

BIBLIOGRAPHY

1. Jolliffe, Norman. The preventive and therapeutic use of vitamins. *J.A.M.A.* 129:613, 1945.
2. Turner, Dorothea. Handbook of Diet Therapy. Chicago, Univ. Chicago Press, 1946.

Chapter 3

THE CLINICAL SIGNS

Norman Jolliffe, Frederick F. Tisdall, and Paul R. Cannon

THE physical examination for signs of malnutrition consists first, of a thorough medical examination to detect other diseases or conditioning factors which may influence the nutritional status; and second, of a special examination to detect clinical signs which in themselves may be directly significant in the identification of deficiency diseases. The examination form in use at the Nutrition Clinics of the Department of Health of the City of New York (Table 12) may serve as a guide for recording pertinent findings. In Table 13 the various clinical findings are grouped with the deficiencies or syndromes which they suggest. The detailed descriptions of the development of the various clinical pictures are given in the chapters dealing with each of the nutrients. In the present chapter brief clinical descriptions and illustrative photographs of the more common signs, both early and late, will be presented.

Most physicians are familiar with the signs of advanced florid deficiency disease as they occur in classical starvation, protein deficiency, osteomalacia, rickets, scurvy, pellagra, and beriberi. Most malnutrition, however, is not of this advanced, easily recognized variety but is manifested by signs less fully developed, less severe, or less acute than the classical textbook descriptions imply. These lesser signs are frequently overlooked. Consequently much malnutrition remains unrecognized even when it is sufficiently advanced to cause anatomic changes detectable without the aid of laboratory or other special technics. The purpose of the present chapter is to aid the physician in recognizing these signs as early as is

TABLE 12. EXAMINATION FORM

NUTRITION CLINIC, DEPARTMENT OF HEALTH, CITY OF NEW YORK

DATE

HAIR: Normal, dry, staring, pediculosis, greyness

SCALP: Alopecia, seborrheic eczema

SKIN: Normal

Acne: None, greasiness, comedones, papules, pustules, nodules, acne rosacea, acne varioliformis

Follicular hyperkeratosis:

Smooth: Avascular, vascular, pustular, hemorrhagic

Rough: Avascular, vascular, pustular, hemorrhagic

Xerosis: Dry, crinkling, ichthyosis

General: Intertrigo, vitelligo, scleraderma, eczema, petechiae, hematoma, spider telangiectasia, liver palms, naevi

Dyssebacia: (Specify site)

Nails:

Other:

EYES: Normal U

Lids: Normal, marginal blepharitis L

follicular hypertrophy, edema

Canthi: Normal, pigmentation, dermatitis, fissures

Lashes: Normal, diminished, absent

Conjunctiva: Thin, thickened, gross spots, pterygia, grade__________

Cornea: Arcus

Suborbital pigmentation: present, absent

LIPS: Normal, chapping cheilosis, atrophic cheilosis, increased vertical fissuring

ANGLES: Stomatitis, fissures, La perleche, scarring

GUMS: Normal, marginal gingivitis, general gingivitis, hypertrophy, atrophy, sponginess, recession, retraction (pocketing), blunted papillae, spontaneous bleeding, pressure bleeding

BUCCAL MUCOUS MEMBRANES: Normal, scarlet red, beefy red, ulcers, Vincent's infection, lichen planus, leukoplakia

TONGUE: Normal

Color: Normal, scarlet red, beefy red, magenta, other

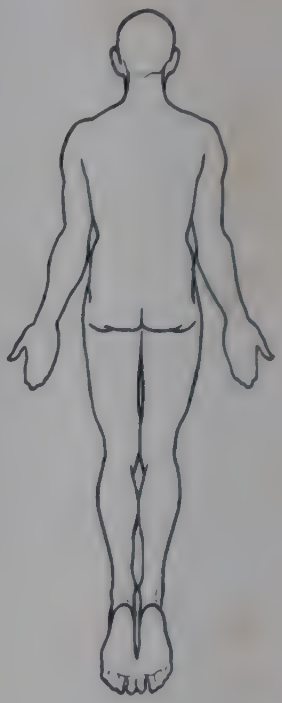
Papillae: Fungiform: hypertrophy, mushrooming, atrophy, fusion

Filiform: hypertrophy, mushrooming, atrophy, fusion

Fissures: Central, central with branches, multiple, cobblestone

General: Hypertrophy, atrophy, edema, serration, ulcers

SKELETAL: Normal, pot belly, flared scapulae, bowed legs, knock knees, frontal bosses, pigeon breast, Harrison's groove, beading of ribs, flat chest, depressed xiphoid, lordosis, kyphosis, scoliosis



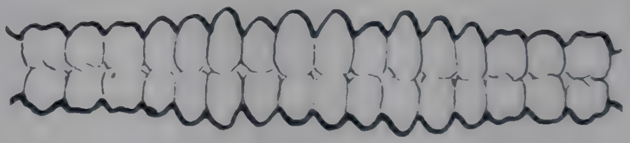


Table 12. *(Continued)*

Date

Neurological:
Plantar dysesthesia
Calf muscle tenderness
Knee jerks
Ankle jerks
Babinski
Vibration sense
Position sense
Nystagmus

Head:

Neck:

EENT:

Heart:

Lungs:

Abdomen:

Extremities:

Glands:

Blood Pressure:

Signature______________________________

Diagnosis:

Anatomical	Nutrient Deficiency	Velocity	Etiology
1.			
2.			
3.			
4.			
5.			

Recommended Therapy:

Signature______________________________

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Table 13. CLINICAL FINDINGS AND SUGGESTED DEFICIENCY OR SYNDROME*

Findings	*Suggested deficiency or syndrome*
General	
Underweight Underheight } (T)†	Calories, protein, calcium, phosphorus, vitamins
Pallor (T)	Iron, folic acid, vitamin B_{12}, ascorbic acid, thiamine, B-complex
Hair	
Dry, staring hair, usually with pediculi (N)	Unknown
Skin	
Perifolliculosis (N)	Ascorbic acid, unknown
Follicular hyperkeratosis	Vitamin A, unknown
Xerosis (N)	Vitamin A, unknown
Dermatitis of pellagra (N)	Niacin
Erythematous	
Intertriginous	
Hyperkeratotic	
Ichthyotic	
Dyssebacia, especially in nasolabial folds, external canthi, behind ears and in body folds (N)	Riboflavin, unknown
Intertrigo (N)	Niacin, riboflavin, unknown
Acne (T)	
Acne vulgaris	Unknown, riboflavin, pyridoxine, vitamin A
Acne rosacea	Unknown, riboflavin
Acne varioliformis	Unknown
Palmar erythema	Unknown, B-complex, riboflavin, amino acids
Spider telangiectasis	Unknown
Suborbital pigmentation (T)	Unknown
Hemorrhagic manifestations (N)	Ascorbic acid, vitamin K, unknown
Eyes	
Bitot's spots	Vitamin A
Corneal vascularity	Unknown, riboflavin
Circumcorneal injection	Unknown, riboflavin
Rosacea keratitis	Unknown, riboflavin
Follicular conjunctivitis	Vitamin A, unknown
Scarlet conjunctivitis (T)	Niacin
Blepharitis (T)	Unknown, vitamin A, riboflavin
Canthi fissures (T)	Riboflavin, unknown
Night blindness	Vitamin A
Photophobia (T)	Vitamin A, riboflavin
Lips	
Cheilosis	Riboflavin, B-complex, pyridoxine
Chapping (N)	Unknown
Increase in vertical fissuring	
Atrophic cheilosis	
Angular stomatitis (N)	Riboflavin, B-complex, iron
Angular fissures (N)	Riboflavin, B-complex, iron
La perleche (N)	Riboflavin, B-complex, iron

TABLE 13. (*Continued*)

Findings	*Suggested deficiency or syndrome*
TONGUE	
Scarlet red glossitis (N)	Niacin, folic acid, vitamin B_{12}, protein
Beefy red glossitis (N)	Niacin, B-complex, folic acid, vitamin B_{12}, protein
Magenta glossitis (N)	B-complex, riboflavin
Chronic glossitis of malnutrition (N)	Niacin, folic acid, vitamin B_{12}, B-complex, protein, unknown
Edema of the tongue (N)	Niacin, unknown
ORAL MUCOUS MEMBRANES	
Scarlet stomatitis (N)	Niacin
Lichen planus	Unknown
Leukoplakia	Unknown
TEETH AND GUMS	
Caries (N)	Unknown
Malocclusion (T)	Vitamin D, unknown
Scorbutic gums (N)	Vitamin C
Gingivitis	Vitamin C, unknown
SKELETAL	
Rachitic deformities (N)	Vitamin D, calcium, phosphorus
Osteomalacia	Vitamin D, calcium, phosphorus
NERVOUS	
Nutritional polyneuropathy	Thiamine, B-complex
Retrobulbar neuritis	Thiamine, unknown
Central ophthalmoplegia	Thiamine
Encephalopathic states	Thiamine, niacin, B-complex, unknown
Combined system disease	B-complex, vitamin B_{12}
Organic reactive psychoses	Thiamine, niacin, B-complex, unknown
CIRCULATORY	
Beriberi heart disease	Thiamine
Edema (T)	Protein, thiamine, famine
ENDOCRINE	
Simple goiter	Iodine

* Reprinted with slight modification by permission from Quarterly Bulletin, Dept. of Health, City of New York, June 1947.

† Teachers (T) or nurses (N) may be instructed to detect appearance of these signs.

consistent with our present knowledge and without the use, in most instances of specialized technics.

To avoid repetition in each of the succeeding sections, it is desirable to emphasize at once four important points.

1. With few exceptions, the signs are *nonspecific* and according to most authorities may be produced by factors other than malnutrition. No single sign is necessarily diagnostic, still less pathognomonic; each must be evaluated in the light of the history and of the other signs and

GROUP I: CUTANEOUS CHANGES ASSOCIATED WITH VITAMIN A DEFICIENCY

The cutaneous changes associated with vitamin A deficiency consist essentially of follicular hyperkeratosis and xerosis, either singly or together. Follicular hyperkeratosis is characterized primarily by an epithelial metaplasia of the hair follicles associated with changes in the sebaceous glands. Various degrees of involvement resemble conditions which are designated by the dermatologist as phrynoderma, keratosis pilaris, keratosis follicularis, and lichen spinulosus. When they first appear (I*a*) they resemble the "goose flesh" seen on chilling, from which they must be differentiated. On briskly rubbing the skin "goose flesh" disappears, while follicular hyperkeratosis remains. Fully developed lesions (I*g*) consist of symmetrically distributed rough, horny papules formed by keratotic plugs projecting from hypertrophied hair follicles often containing coiled or unerupted hairs.

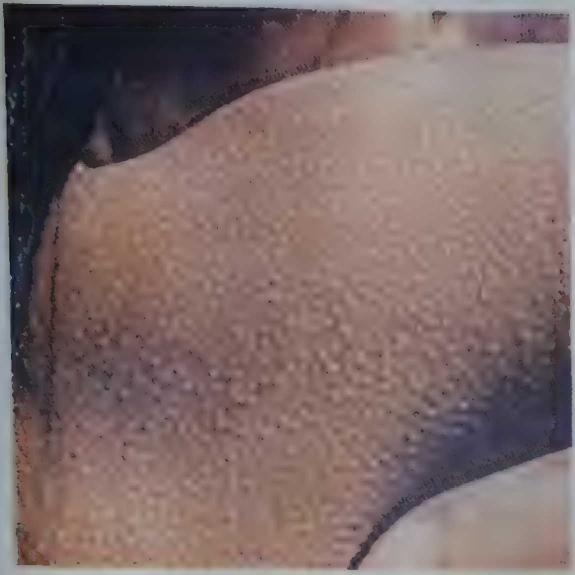
As a rule the lesions first appear on the lateral surface of the arm and the extensor surface of the thigh. As they become more widespread, larger areas of the arm and thigh, and later the skin of the forearms, legs, shoulders, buttocks, back, and abdomen, become involved. In advanced follicular hyperkeratosis the skin of almost the entire body may be affected. As the result of suppression of the cutaneous secretions, the skin becomes dry.

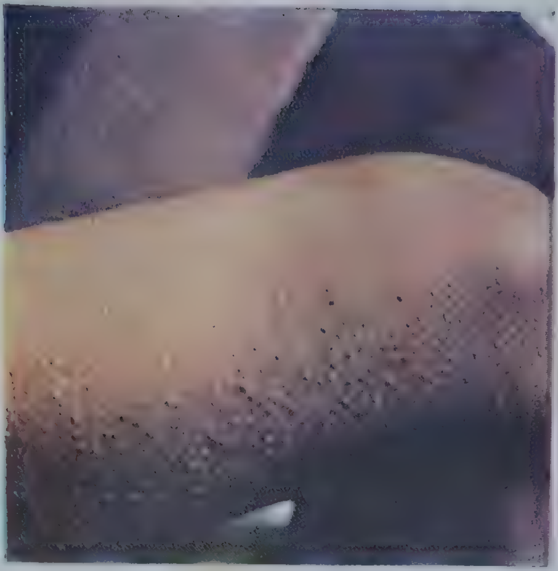
Differentiation must be made from the follicular involvement of acne vulgaris, adolescent folliculitis, the folliculitis from dirt and from chemical agents used in industry, and follicular involvement in ascorbic acid deficiency. It must be differentiated also from the "goose flesh" resulting in part from atrophy of the tissues adjacent to the follicles and seen in severe caloric deficiency. Acne vulgaris is characterized by the presence of papules, pustules, nodules, and comedones, by the moisture and greasiness of the skin, and by the greater involvement of the skin of the

---

GROUP I.

I*a*. Early follicular hyperkeratosis resembling "goose flesh." Texas, U.S.A.
I*b*. Late follicular hyperkeratosis in keratosis follicularis stage: note the horny plugs. Tennessee, U.S.A.
I*c*. Early xerosis or "crinkled" skin: disappears in warm weather. Newfoundland.
I*d*. Intermediate xerosis: note mosaic or pavement-like appearance. Utah, U.S.A.
I*e*. Advanced xerosis: usually called ichthyosis. Newfoundland.
I*f*. Mixed xerosis and follicular hyperkeratosis: often called ichthyosis follicularis. New York, U.S.A.





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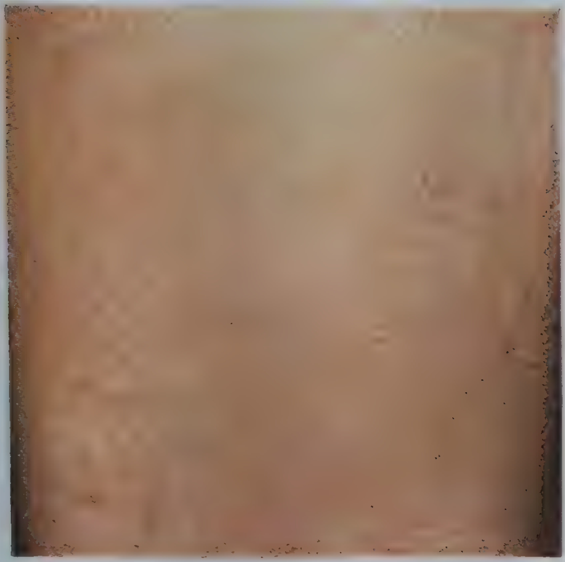

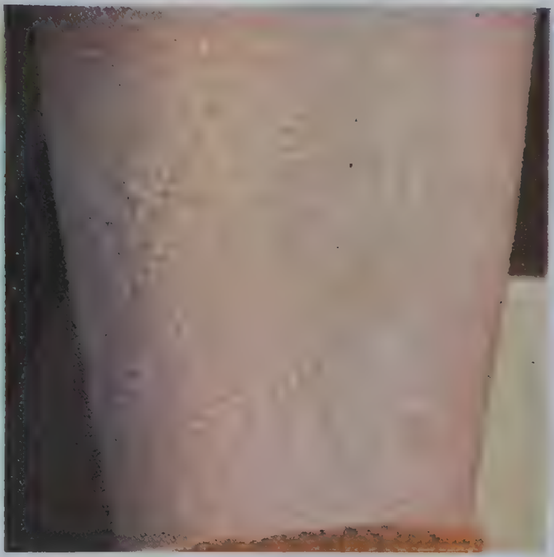

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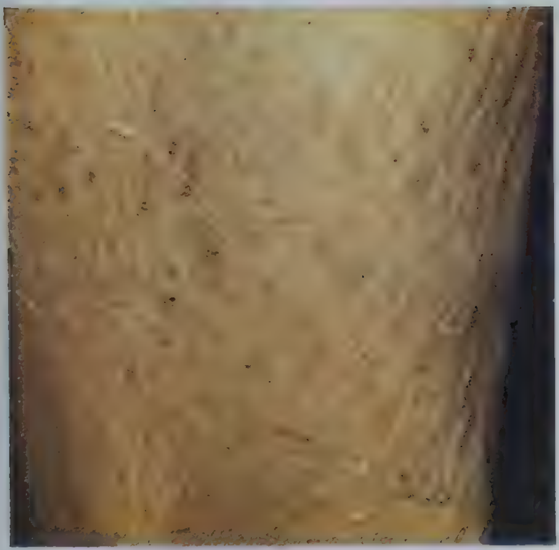

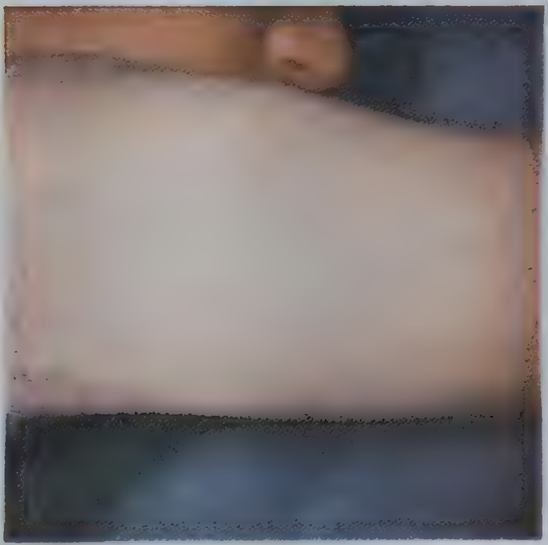

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Group I

face and back. Adolescent folliculitis affects primarily the face and back as contrasted with involvement of the arms and thighs in vitamin A deficiency. A tendency toward increased oiliness characterizes adolescent folliculitis and acne vulgaris. Dirt and chemicals as the causes of folliculitis will be suggested by the history. Capillary congestion around each of the hair follicles is thought by some to suggest ascorbic acid deficiency.

Xerosis is the clinical term used to describe dry and crinkled skin. In severe forms it resembles ichthyosis, or "fish skin" disease, and "alligator skin" disease. In the early stages (I*c*), when the lesion is not yet fully developed, the skin is dry and slightly crinkled. Pushing the skin with the finger parallel to its surface causes accentuation of the crinkling. In more advanced xerosis the fish- or alligator-scale-like distribution of the crinkles is evident (I*d* and I*e*). Early in the course of the disease xerosis may not be detected in warm weather if perspiration moistens the skin sufficiently to prevent or obliterate the crinkling. As the disease progresses, warm weather may fail to obliterate the signs. When the disease is mild it involves only the extensor surface of the limbs, particularly the legs. Advanced xerosis, however, may involve the entire body.

Differentiation must be made from xerosis due to aging, androgen deficiency, hypothyroidism, dirt, or exposure. These conditions often can be suspected from other evidence. Ichthyosis of congenital or of unknown origin is a rather common variety.

Mixed lesions consisting of follicular hyperkeratosis and xerosis are far more common than either alone and are often designated as ichthyosis follicularis (I*f*). Associated with this combination is a thickening and drying of the palms and soles, with accentuation of the normal creases. A common clinical picture consists of follicular hyperkeratosis involving the lateral aspects of the arms and the extensor surfaces of the thighs, with progressive increase of xerosis of the legs from the knee to the ankle, and with thickening and drying of the skin of the palms and soles.

GROUP II: CUTANEOUS CHANGES ASSOCIATED WITH RIBOFLAVIN DEFICIENCY

Dyssebacia is the clinical term used to designate a series of disturbances of the sebaceous glands, characterized by an increase in oiliness and associated with dermatitis, fissuring, filiform excrescences, and "shark skin." The areas affected are those most profusely supplied with sebaceous glands—such as the nasolabial folds, the mid-portion of the face, the forehead, over the sternum, and between the shoulder blades—and the various folds of the body, such as those behind the ears, at the external canthi of the eyes, beneath the breasts, in the intergluteal region, and in the axillae and groins. Skin showing an increase in oiliness (seborrheal type of skin) from a variety of causes, including riboflavin deficiency, is susceptible to infection and is often the site of eczematous manifestations.

After an increase in oiliness the earliest lesions of dyssebacia consist of greasy, yellowish flaky scales on a mildly erythematous base. These usually appear in the nasolabial folds (II*a*) but may occur initially behind the ears (II*e*), lateral to the external canthi (II*f*), and less frequently in other sebaceous areas. This early stage of the disease is usually called nasolabial or canthal dermatitis, or seborrhea. When it extends considerably beyond the original lesion (II*b*) it is usually termed seborrheic eczema. After the flaking, either filiform excrescences or fissures or both occur. The filiform excrescences may be sparsely to densely distributed in the seborrheal areas; they generally appear first on the nasolabial folds and frequently are seen on the mid-portion of the face and forehead. On casual inspection these filiform lesions resemble urea or "hoar frost" but cannot be rubbed off. At times the filiform excrescences in the nasolabial folds become prominent and so packed as to resemble warty excrescences (II*c*). Still later, innumerable plugs of inspissated sebum projecting from dilated orifices of the sebaceous follicles, particularly when occurring over the nose, cheeks, and fore-

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GROUP II.

II*a*. Early dyssebacia in nasolabial fold: note scales on erythematous base. New York, U.S.A.

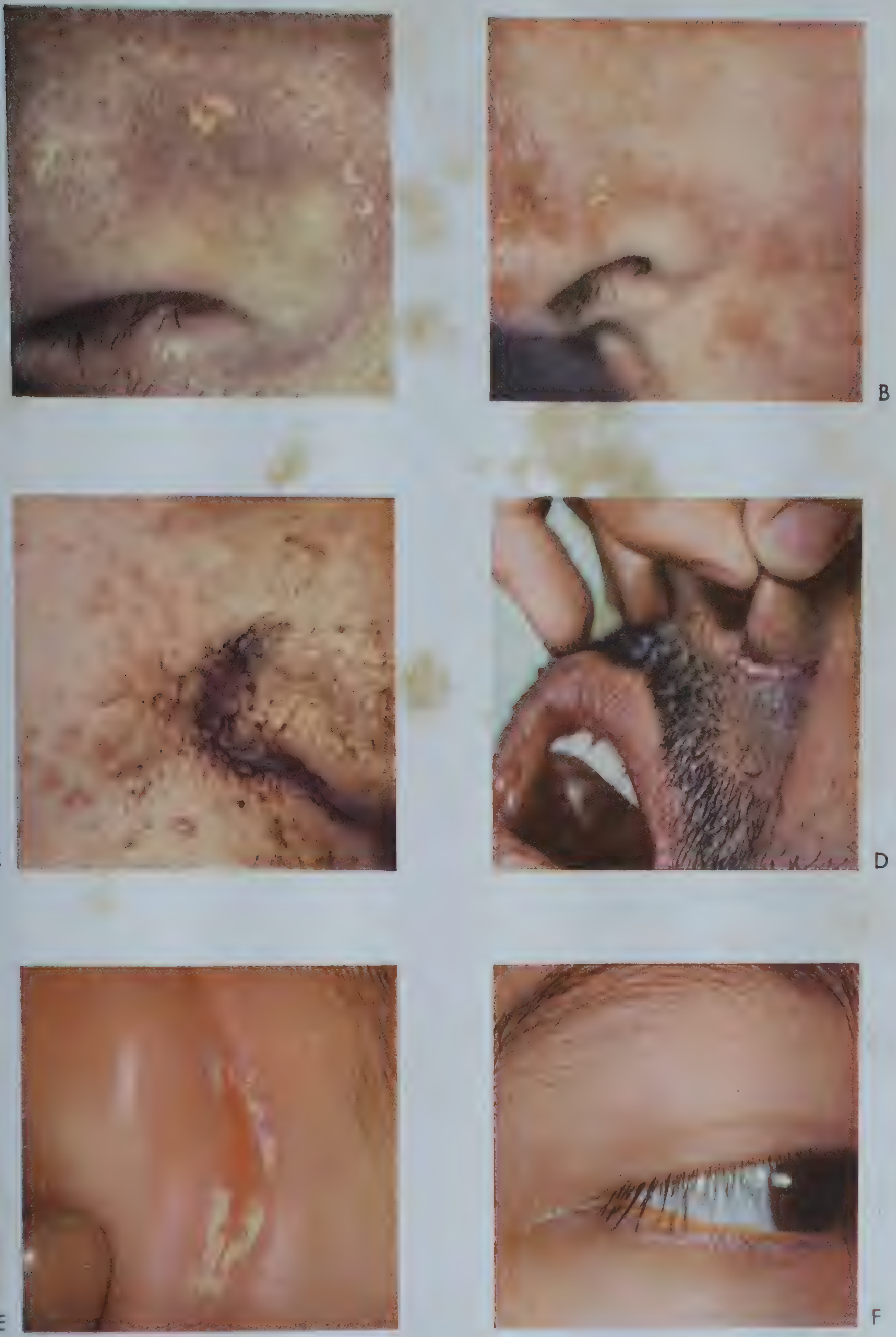
II*b*. Advanced dyssebacia with seborrheic dermatitis. New York, U.S.A.

II*c*. Advanced dyssebacia with "shark skin" dermatitis. New York, U.S.A.

II*d*. Advanced dyssebacia: note partial detachment of alae nasorum. New York, U.S.A.

II*e*. Early dyssebacia with fissuring behind ear. New York, U.S.A.

II*f*. Dermatitis lateral to external canthus, and blepharitis of lower lid. New York, U.S.A.



Group II

ead, give the characteristic "shark skin" sometimes found in patients with pellagra (II*c*). Fissures are likely to occur in the nasolabial folds (II*d*) and behind the ears (II*e*). In late stages these fissures between the alae nasorum and the upper lip may become a half centimeter or more deep so that the alae nasorum can be lifted from the face (II*d*).

Differential diagnosis of dyssebacia from the cutaneous lesions of vitamin A deficiency is made primarily by the presence of oiliness in dyssebacia and dryness in follicular hyperkeratosis and xerosis. The sites of predilection are also different. Causes for dyssebacia or seborrheic dermatitis other than riboflavin deficiency must be excluded. The presence of other lesions suggestive of riboflavin deficiency, such as cheilosis and glossitis, and the history of a diet inadequate in riboflavin, should be considered. Finally, a therapeutic trial of riboflavin may confirm the diagnosis.

In adolescents the increased oiliness of the skin and the mild inflammatory reactions of acne may involve the nasolabial folds and be confused with the dyssebacia of riboflavin deficiency. The age, the presence of other acneform lesions, and the absence of lingual or lip lesions would support a diagnosis of acne.

GROUP III: THE CUTANEOUS LESIONS OF PELLAGRA

The cutaneous lesions of pellagra are variable both in form and in distribution because of differences in conditioning factors, acuteness, degree of nutritional deficiency, and color. In spite of the diverse manifestations, a presumptive diagnosis of pellagra can often be made by the cutaneous lesions alone, leaving the confirmation to other signs and to the history.

There are four types of cutaneous lesions: the erythematous and the intertriginous, which are acute; the hypertrophic and the ichthyotic, which are chronic.

The first and most acute is an erythematous type (III*a*). The erythema is followed by vesiculation or formation of bullae, crusting (III*b*), and desquamation. The vesicles and bullae frequently become infected. The main point of distinction between the erythema in a pellagrin and in a normal person is the amount of solar exposure necessary to produce it. Degrees of light that would give a healthy tan in a normal person give a pellagrin an erythema with subsequent exudative changes.

The second type of acute skin lesion is the intertriginous (III*c*). It is essentially a lesion resulting from chafing, characterized by redness, maceration, abrasion and, often, superimposed infection. These lesions can be, and often are, induced by heat, friction, moisture and lack of personal hygiene, which in the pellagrin serve as conditioning factors, just as solar trauma induces erythema.

The third and more common form of chronic cutaneous lesion of the pellagrin is the hypertrophic (III*d*). The skin becomes thickened, inelastic, fissured and, over the joints, deeply pigmented. This lesion represents the response of the skin of a pellagrin to trauma repeated from light or other causes, over a long period. Infection is often superimposed. The terminal phalanges and the palms are seldom involved. When healing starts, the margins of the cutaneous lesion show a sharply defined pearly border of regenerating epithelium.

The fourth form of pellagrous skin lesion, also chronic, is the atrophic or ichthyotic (III*e*). The skin becomes dry, scaly, atrophic, inelastic, and

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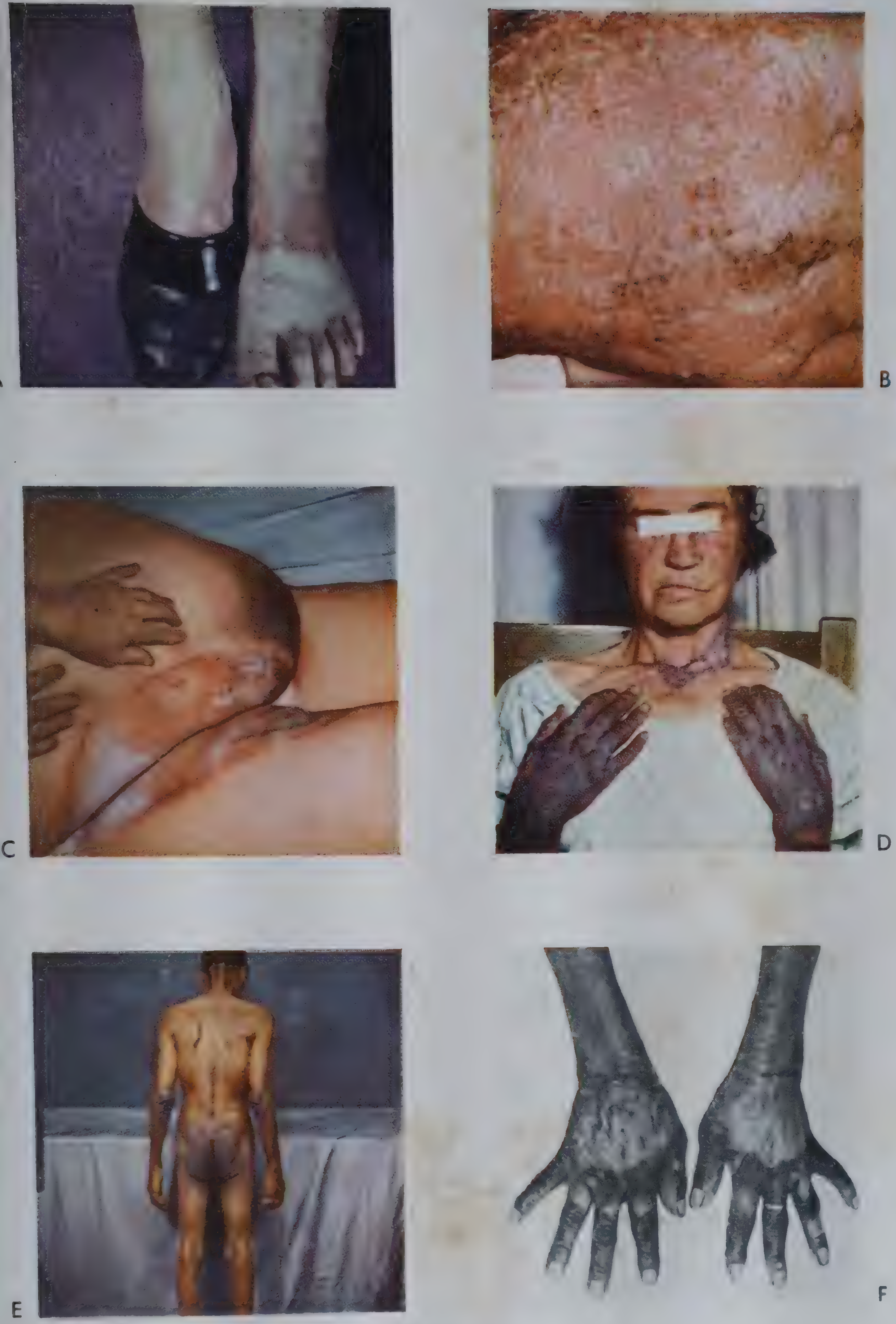
GROUP III.

III*a*. Erythema of pellagra: a response to solar trauma. Georgia, U.S.A.
III*b*. Acute dermatitis of pellagra: exudative changes on dorsum of hand after solar erythema. New York, U.S.A.
III*c*. Intertrigo of abdominal apron in an obese pellagrin. New York, U.S.A.
III*d*. Hypertrophic dermatitis of pellagra. New York, U.S.A.
III*e*. Atrophic dermatitis of pellagra. Alabama, U.S.A.
III*f*. Depigmentation in a Negro after acute dermatitis of pellagra. South Africa.



GROUP III

often too big for the body contained in it. This type of skin is found as a rule in older pellagrins.

Although each of these four forms of lesion occurs alone, mixed forms are common, and it is not rare to see two or more types in the same patient. They are also associated with variable disturbances of pigment which may persist for years after the dermatitis has disappeared, although erythematous lesions may heal without residual pigmentation. Depigmentation is common in the Negro (III*f*).

The distribution of the pellagrous skin lesions is more characteristic than the form. They occur at the trauma points of the body. From actinic trauma the dermatitis occurs on the face in a butterfly distribution, on the back of the hands, and on other exposed parts of the extremities and body. Casal's "necklace" (III*d*) occurs in women wearing low necked dresses and in men who wear the shirt collar open. If the individual goes stockingless the dorsum of the feet and ankles (III*a*) become involved where protection is not afforded by the clothing. The pressure points most commonly affected are the elbows, the ischial tuberosities, and the knees. The intertriginous areas are under the breasts, between the nates, in the groin, and on the scrotum, axillae, flexures of the skin folds, and other fleshy folds in fat people (III*c*).

The cutaneous lesions are most frequently symmetrical, but unilateral lesions are sometimes seen.

GROUP IV: MANIFESTATIONS OF SCURVY IN THE SKIN AND GUMS

The clinical picture of scurvy is somewhat different in the adult than in the infant because of the presence of body hair in the former and of rapid growth and development in the latter. In infants the disease appears in the majority of cases between the sixth and twelfth month. The characteristic signs of manifest scurvy in the infant are: irritability, pain on movement of the extremities, angular enlargements of the costochondral junctions, swelling of the extremities over the ends of the bones (particularly of the lower end of the femur) but not extending into the joints, and a tendency to hemorrhage as evidenced by hemorrhagic gums surrounding the erupting teeth and by cutaneous ecchymoses and petechiae under the skin. Roentgenographic changes characteristic of the disease are illustrated in XII *c* and *d*, and the scorbutic rosary is illustrated in XV*a*.

In adults the disease is characterized by a long latent period (three months to a year or longer) of a severe inadequacy of ascorbic acid (vitamin C) in the food. Manifest scurvy in the adult is often preceded by a loss of weight. Swelling of the gingivae and their loosening from the teeth occur early in adults with teeth. During this period intercurrent infection is likely to precipitate the classical picture. Muscle hemorrhages, particularly massive ones, are more common than in the infant, but hemorrhages around the epiphyses where rapid bone growth is taking place in the infant do not occur in the adult. Perifollicular congestion (IV*a*) is common in the adult but is never seen in the infant. Subperiosteal hemorrhages, cutaneous petechiae and purpura, and hemorrhages into the gums occur in both infants (IV*e*) and adults (IV*f*).

The manifestations of scurvy in the skin consist of perifollicular congestion, petechiae, purpura, and hematomas, all of which are dependent upon increased capillary fragility secondary to defective formation of intercellular cement substance. Stress determines the site of the lesions. For example, the trauma of the blood pressure cuff (IV*b*) or the pressure

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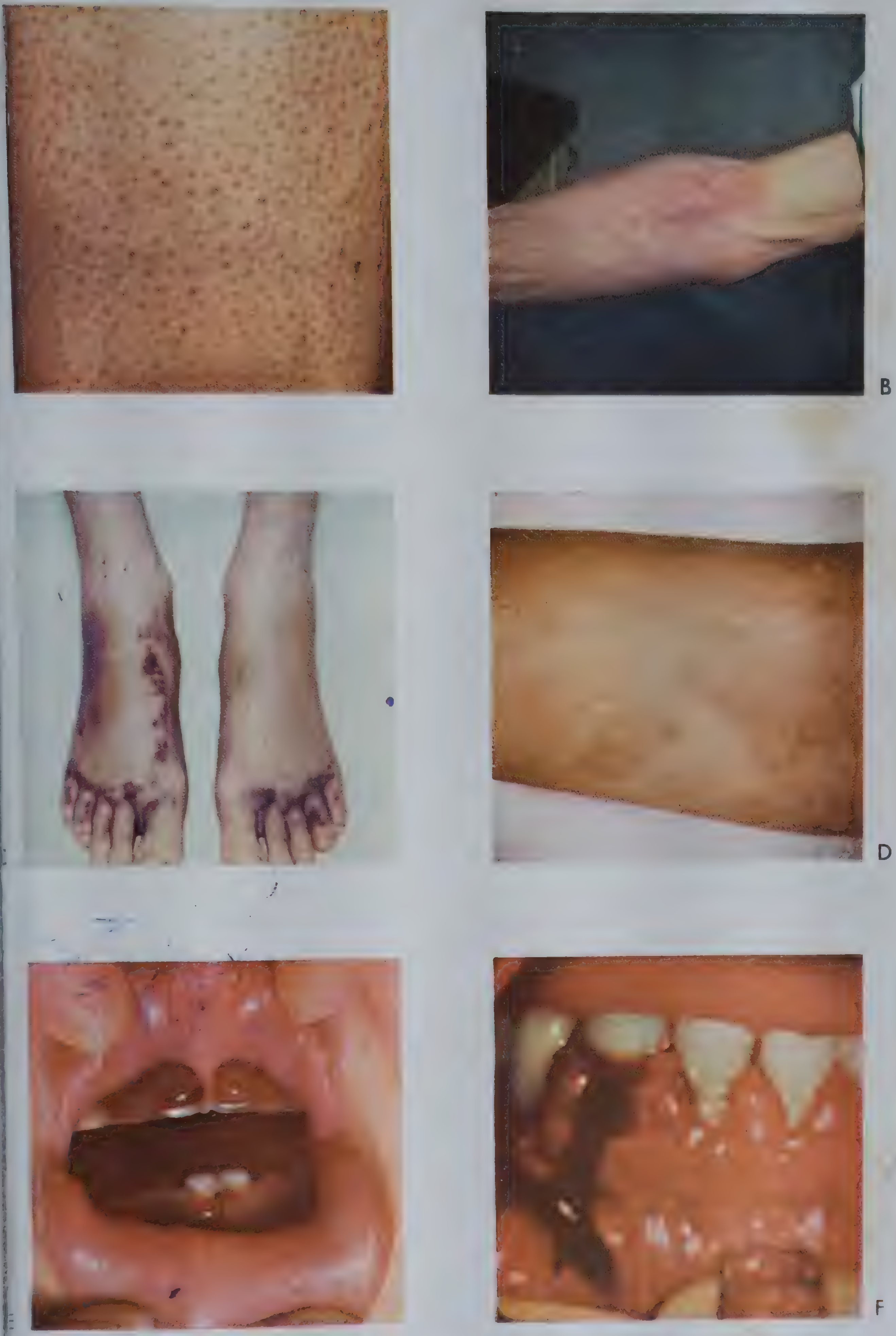
GROUP IV.

IV*a*. Perifolliculosis: note congestion about each hair follicle. Newfoundland.
IV*b*. Petechiae in a scorbutic patient following application of blood pressure cuff. New York, U.S.A.
IV*c*. Purpura in a scorbutic patient from pressure of shoes. Texas, U.S.A.
IV*d*. Purpura and petechiae in a scorbutic patient. Manitoba, Canada.
IV*e*. Scorbutic gums in an infant. Ontario, Canada.
IV*f*. Scorbutic gums in an adult. Manitoba, Canada.



Group IV

of shoes (IV*c*) or an accidental bruising too slight to be remembered (IV*d*) often determines the location of the lesion.

In perifolliculosis (IV*a*), congestion and other changes occur around the hair follicles. It is therefore limited to the hairy regions of the body and, more frequently, to the dependent parts such as the legs and forearms. After the perifollicular congestion, swelling and hypertrophy of the follicles occur, at which time the skin is rough (IV*a*). Early perifolliculosis is to be distinguished from the early stages (I*a*) of follicular hyperkeratosis. In the more advanced stage, when keratosis has developed, it is also to be differentiated from the similar skin changes of vitamin A deficiency. It must be remembered that the follicular hyperkeratosis of vitamin A deficiency and the perifollicular congestion of ascorbic acid deficiency often coexist.

Petechiae (IV*b*) often occur in scurvy either spontaneously or following blood pressure determination or the application of a tourniquet. Petechiae simply indicate increased capillary fragility from any cause and are not diagnostic of scurvy.

The same applies to purpura and hematomas (IV*c* and *d*).

Rapidly developing hemorrhages into the gum tissues surrounding the teeth characterize scorbutic gums in both the infant (IV*e*) and the adult (IV*f*). In the infant, particularly, the gingivae appear to consist of bags of blood, sometimes so large as to cover the teeth. Slight pressure will rupture them, sometimes causing profuse but not dangerous bleeding. Treatment of acute scorbutic gums with adequate amounts of ascorbic acid results in obvious clinical improvement in two or three days and absorption of most of the blood and edema fluid within one to two weeks. In adults, acute scorbutic lesions often are superimposed on chronic gingival lesions (see Group V).

GROUP V: INFLAMMATORY CHANGES IN THE GINGIVAL TISSUES

Inflammatory changes in the gingival tissues are found with great frequency in many population groups throughout the world.

Normal gingival tissue is characterized by its light pink color. The interdental papillae fill the interdental spaces neatly and, with the remainder of the marginal gum tissue, are in firm contact with the teeth but not attached to them. The free margin of the gum may be up to 2 mm. in depth, but the remaining gingival tissue is firmly attached to the tooth and bone (V*a*).

The first sign of gingival inflammation is usually seen in the marginal gum tissue, most frequently in the interdental papillae. It is characterized by swelling, redness, tenderness, and bleeding on pressure (V*b*). The involved gum tissue usually has a shiny appearance due to the swelling. As the condition progresses over many months, the swelling and redness become more marked and, instead of involving only the marginal area, extend over the labial and buccal gingival areas (V*c*). Examination with a probe will show that the deeper gum tissue, which ordinarily is firmly attached to the teeth, has become detached, allowing the probe to be inserted to a depth of several millimeters between the gum tissue and the surface of the tooth. A still more severe degree of the same condition is shown in V*d*. As a result of the gradual extension of the process, or after periodic exacerbations, extensive detachment of gum tissue and destruction of the bony support of the dental root occur (V*e*), with eventual loss of the affected teeth.

In the progression of the chronic changes the gums become thickened and pale and develop a hard, leathery consistency. The impression is obtained of an increase in fibrous tissue. Unless the acute changes are

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GROUP V.

V*a*. Normal gums: color light pink, papillae pointed; no swelling, thickening, or inflammation. Royal Canadian Air Force.

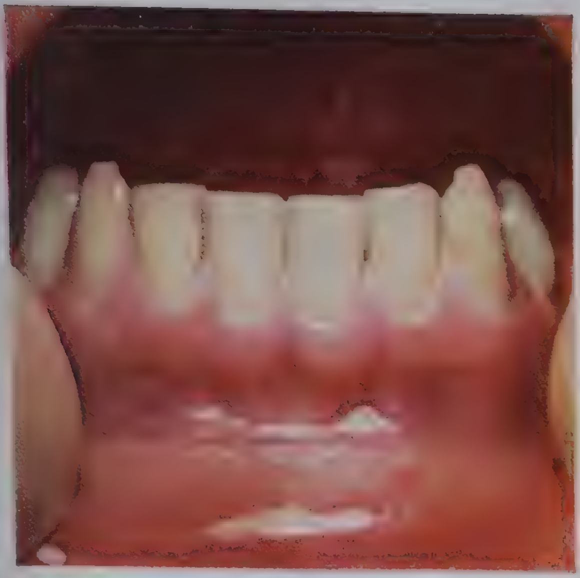
V*b*. Mild gingivitis: redness and swelling of papillae and marginal gingivae. Royal Canadian Air Force.

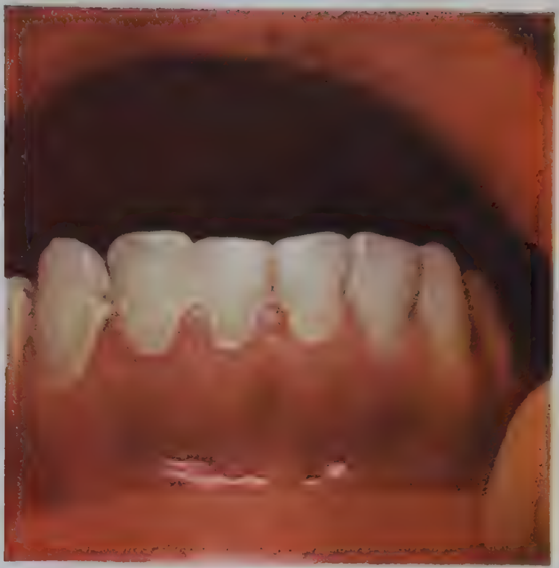
V*c*. Moderate gingivitis: more marked redness and swelling of gingivae. Royal Canadian Air Force.

V*d*. Advanced gingivitis: marked swelling of papillae with loss of tissue and retraction. Newfoundland.

V*e*. Hypertrophic gingivitis: contrast with gingival destruction. Ontario, Canada.

V*f*. Gingival destruction resulting from gingivitis. Royal Canadian Air Force.





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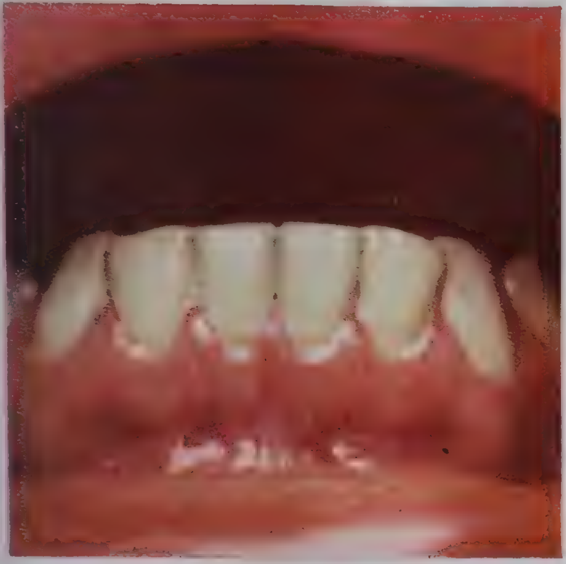

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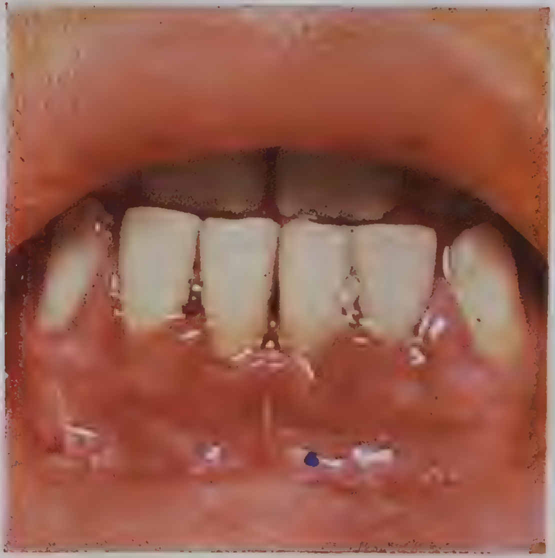

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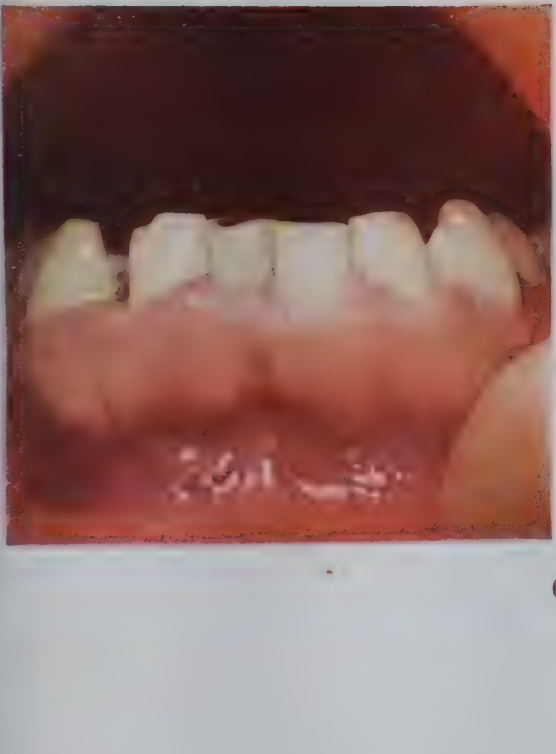

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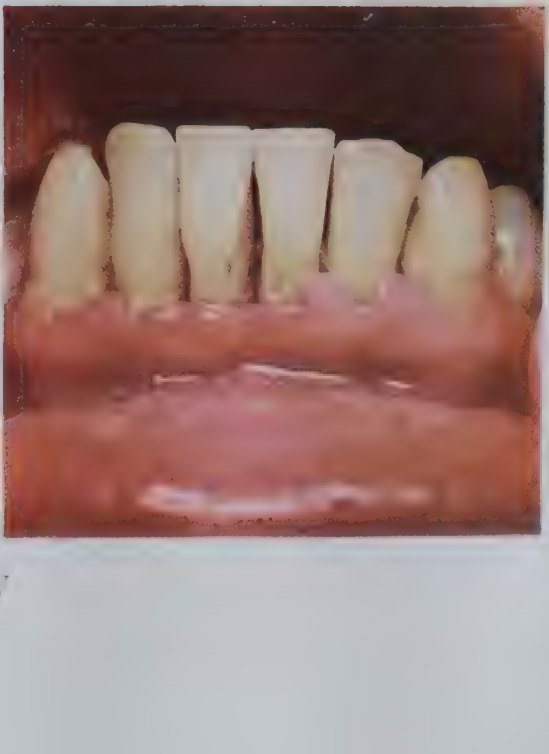

F

GROUP V

superimposed, which often occurs, the gum tissue in the chronic form, although thickened, does not present a shiny surface (V*f*).

Many factors, local and general, nutritional and non-nutritional, are probably concerned in the development of these changes in the gums. Local factors such as malocclusion can increase the stress on certain areas of gum and tooth-supporting tissue. It is possible that softness of the food with resultant lack of local stimulation also may affect the gingival tissue. Infection of the gingival tissue secondary to excess tartar formation is probably the most important conditioning factor. Nutritional factors most commonly mentioned as deficient are ascorbic acid and some of the B vitamins.

Suggestive evidence that a low intake of ascorbic acid influences the development of gingivitis is the fact that in certain countries, such as Newfoundland, where the average daily intake of ascorbic acid (vitamin C) is low, gingivitis is almost universally seen; whereas in other areas, such as the British West Indies, where the ascorbic acid intake is high although the diet is deficient in other nutrients, gingivitis is seldom encountered. It has been demonstrated that after local treatment of gingivitis a low intake of ascorbic acid (8 to 10 mg. daily) over a period of six months or more was associated with a high incidence of recurrence of the inflammatory gingival changes, while a large intake of ascorbic acid (75 mg. daily) was associated with a low incidence of recurrence. Finally, it has been reported by several observers that gingivitis in many persons responds to ascorbic acid therapy when administered over a period of many months. There are, however, a larger number of studies reporting negative results.

It must be emphasized that the inflammatory gingival changes pictured in Group V are different from the acute hemorrhagic changes which develop in scurvy (IV*e* and *f*). These latter changes are associated with severe deficiency of ascorbic acid over a period of some months, while the gingivitis described in this section when due primarily to malnutrition, is associated with only a partial depletion of nutrients over a longer period. It must be emphasized also that, in most patients, many factors may play a causal role simultaneously with gingivitis, and correction of one factor alone should not be expected to effect a cure.

GROUP VI: COLOR CHANGES IN THE TONGUE IN B-COMPLEX DEFICIENCIES

Three rather typical color changes can be seen in the tongues of persons deficient in B-complex vitamins. These changes are scarlet-red and "beefy-red" glossitis, and the magenta tongue.

Scarlet-red glossitis is characteristic of acute pellagra and sprue. It first affects the papillae on the tip and lateral margins of the tongue and is sometimes associated with redness of the buccal mucosae first noted around the papillae of Stenson's duct. As the lesion progresses, the entire tongue and often all the oral mucous membranes become a bright scarlet red (VI*b*, *c*, and *d*). Associated with the scarlet-red glossitis are increased salivation, soreness of the mouth, and edema of the tongue as shown by tooth indentations on the sides. Ulcerations may appear anywhere in the mouth or throat but they have a special predilection for the undersurface of the tongue, the mucosa of the lower lip, the mucosa opposite the line of closure of the molar teeth, and the gums. These ulcerations are often covered by a grayish slough in which Vincent's organisms abound. Though an acute scarlet-red glossitis may occasionally occur in a previously normal tongue, it is usually superimposed on various grades of chronic glossitis which are illustrated in increasing degrees of severity in VI*b*, *c*, and *d*. In the acute scarlet-red glossitis of pellagra adequate treatment with niacinamide usually results in a dramatic response. The patient notes decrease in soreness within twenty-four to forty-eight hours, and the physician can note the initial fading of the abnormal color within forty-eight to seventy-two hours and its complete disappearance usually within a week.

A similar response occurs in sprue after therapy with vitamin B_{12} and folic acid. Occasionally, however, a scarlet-red glossitis will fail to respond over long periods of time to parenteral administration of all vitamins including folic acid, vitamin B_{12}, and crude liver extract, but

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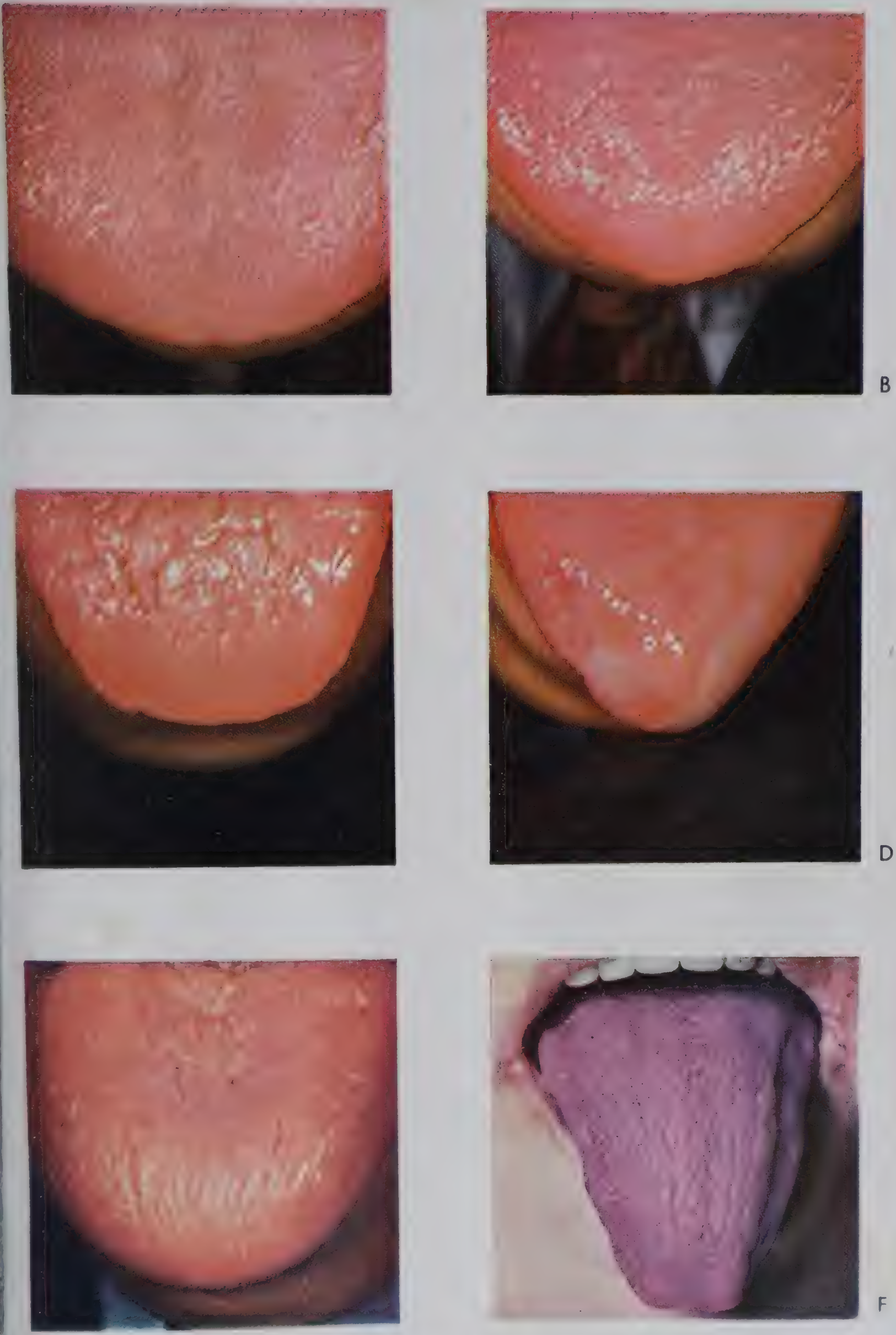
GROUP VI.

VI*a*. Normal tongue for color comparison. New York, U.S.A.
VI*b*. Scarlet red glossitis in a pellagrin with mild chronic glossitis. New York, U.S.A.
VI*c*. Scarlet red glossitis in a pellagrin with marked chronic glossitis. New York, U.S.A.
VI*d*. Scarlet red glossitis in a patient with chronic intestinal obstruction with advanced chronic glossitis. New York, U.S.A.
VI*e*. Beefy red glossitis in a patient with multiple deficiency disease. New York, U.S.A.
VI*f*. Magenta tongue with angular stomatitis and dermatitis. New York, U.S.A.



Group VI

may respond to blood transfusions and protein hydrolysates given intravenously. It may be that some amino acid is necessary in such a patient to complete the enzyme system to which niacin or folic acid belongs, or that amino acid deficiency alone may occasionally produce a scarlet-red glossitis.

Beefy-red glossitis (VI*e*) must be distinguished from the acute scarlet-red glossitis, and the chief clinical point of distinction is the darker color of the former, which resembles raw beefsteak. This lesion probably represents most frequently a subacute deficiency of niacin, and, less frequently, of other fractions of the vitamin B complex that are present in liver or in yeast. Response to adequate therapy may begin within a week or ten days but several weeks or months are usually required for complete fading. Beefy-red glossitis is most often superimposed on chronic glossitis and, next to the latter, is the most common lesion of the tongue seen in a general medical or surgical practice.

Magenta tongue (VI*f*), as its name indicates, is a purplish discoloration of the tongue. It is usually superimposed on a chronic glossitis and its frequent association with angular stomatitis and dermatitis, as well as the therapeutic response, makes riboflavin deficiency suspect.

Occasionally in pellagrins who have an acute scarlet-red glossitis, the magenta tongue can be seen to develop after treatment with niacinamide. The clearing of the scarlet-red glossitis leaves the tongue with a magenta color which may persist for weeks or months.

GROUP VII: STAGES OF CHRONIC GLOSSITIS SEEN IN B-COMPLEX DEFICIENCIES

The earliest lesion of chronic glossitis consists of hypertrophied fungiform papillae in the anterior third of the tongue just posterior to the tip (VII*a*). The end stage is characterized by complete atrophy of both the filiform and fungiform papillae (VII*f*), producing a thin, completely smooth tongue. Between these two stages the papillae go through the following sequence: hypertrophy, flattening of the tips, fusion, and atrophy. Ordinarily the fungiform papillae are involved first, the filiform later. Consequently, innumerable stages of the various combinations of fungiform and filiform papillary hypertrophy, flattening, fusion, and atrophy occur between hypertrophy limited to the fungiform papillae and complete papillary atrophy. As the papillae first involved are the fungiform, and these are most numerous in the anterior third of the tongue, this region not only shows the earliest changes but, in the intermediate stages, the most advanced. The regions successively affected are the anterior third, lateral margins, middle third, and posterior third. After the first stage, limited to hypertrophy of the fungiform papillae, the filiform papillae become involved (VII*b*), producing a thick tongue. Flattening and fusion then occur (VII*c* and *d*). Gross evidence of the papillary flattening is a glazed appearance of the hypertrophied tongue. This may be general if the flattening is widespread, or localized to the areas where the papillae are in this stage. With the hand lens, or better still under the low power magnification of the biomicroscope, the flattened papillae resemble mushrooms or flat-headed rivets. Papillary fusion is evidenced grossly as a furrowing (VII*c* and *d*). Here blocks of papillae are pulled together and fused, forming furrows between the blocks not unlike parting the hair. The fusion of the papillae in blocks parts them into patterns varying from a few furrows with irregular distribution to

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GROUP VII.

VII*a*. Early chronic glossitis with fungiform papillary hypertrophy. New York, U.S.A.

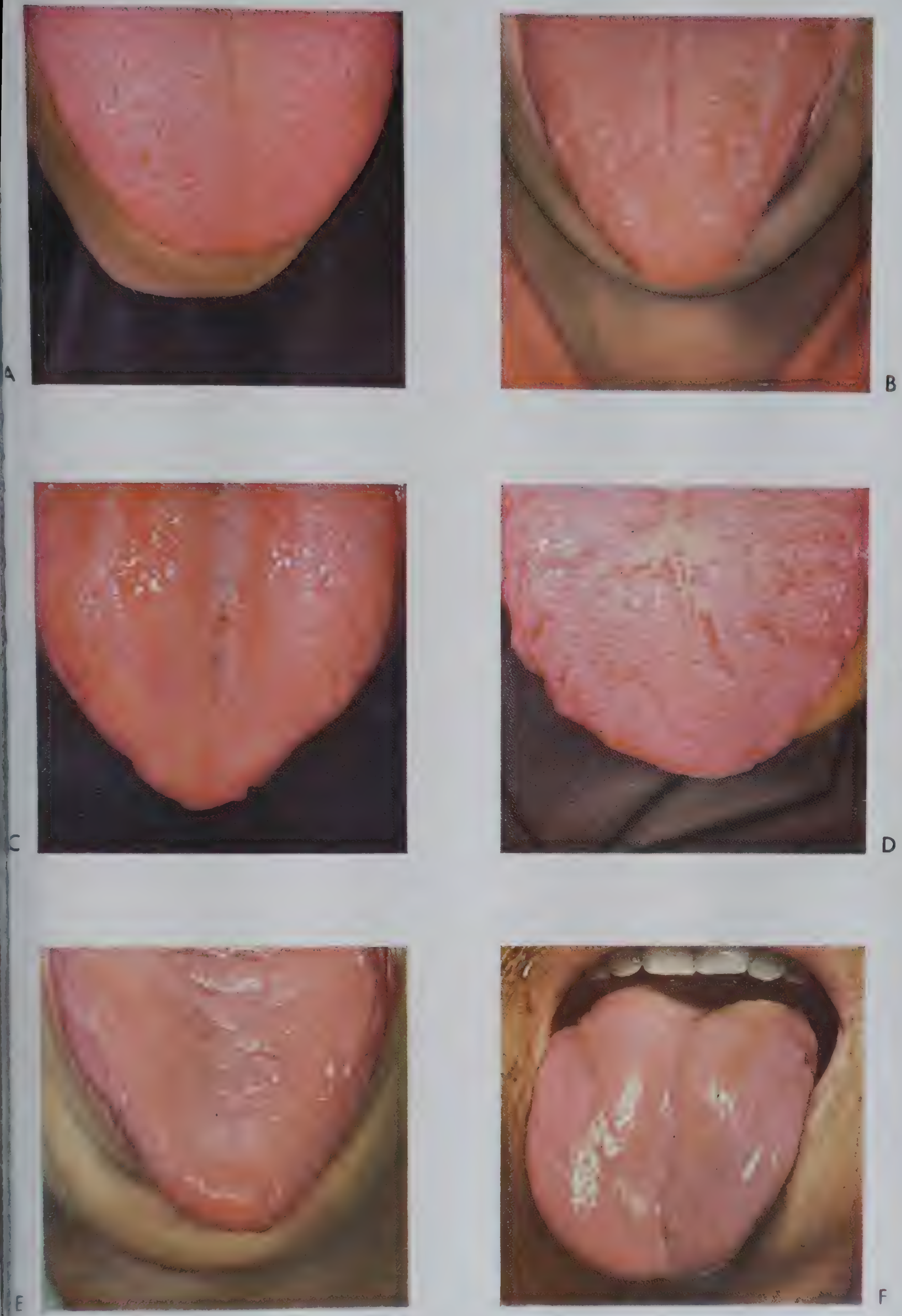
VII*b*. Early chronic glossitis with fungiform and filiform papillary hypertrophy. New York, U.S.A.

VII*c*. Moderately advanced chronic glossitis with papillary fusion. New York, U.S.A.

VII*d*. Moderately advanced chronic glossitis with papillary fusion and early atrophy. New York, U.S.A.

VII*e*. Advanced chronic glossitis with marked papillary atrophy. New York, U.S.A.

VII*f*. Late chronic glossitis with complete papillary atrophy. Newfoundland.



Group VII

innumerable furrows of regular and irregular distribution. Such patterns give rise to the term "geographic tongue." Certain distributions give the tongue a cobblestone appearance, others a scrotal pattern; others appear serrated, while still others are so bizarre as to defy description. Atrophy is manifested first by shortening of the papillae in small areas, usually at the tip and margins, and later by complete loss of the previously hypertrophied papillae (VII*f*). As the atrophy progresses, the furrows become shallower and shallower (VII*e*) and eventually disappear (VII*f*).

The progression of these lesions may be slow or rapid. In some cases only papillary hypertrophy may be noted after many years, while in others only a few weeks or months may elapse between early papillary hypertrophy and complete atrophy. The progress of the disease may stop and may become more or less stationary at any stage. Similarly, a remission with return of the papillae to normal may occur from any stage.

Chronic glossitis has been attributed by various investigators to deficiencies of one or another of the B-complex vitamins, particularly niacin, vitamin B_{12}, riboflavin, and folic acid. However, a furrowed or geographic tongue may exist for years in persons otherwise healthy and in whom there is no other reason to suspect malnutrition. Apparently some of these lesions are congenital or of unknown etiology. Fungus infection may occasionally provoke glossitis in apparently well nourished persons, and leukoplakia and late syphilis must also be differentiated.

GROUP VIII: DENTAL CARIES AND RELATED ABNORMALITIES

Although the exact role played by food and nutrition in the causation of dental caries is controversial, there is no doubt that food can definitely influence its development. There are many examples of people in remote regions, living on fish, game, grains, vegetables, and fruits, who have excellent teeth; yet the younger generation of these people develop rampant caries when they substitute highly milled flour, sugar, and lard for the natural foods. On the other hand when food and nutrition are as they should be and if dental caries develop, it is probable that various oral environmental factors are of primary importance.

Two nutritional factors have been stressed in the production of dental caries. These are, first, that the diet is deficient in one or more essential nutrients, among them vitamin D; and second, that the diet contains an excess of simple carbohydrates, which allows harmful acid-producing bacteria to multiply in proximity to the teeth.

In recent years evidence has been brought forward that the presence of a small amount of fluorine (one part per million) in the drinking water used during the first decade of life tends to reduce the incidence of dental caries.

Dental caries develop at an early age in the deciduous teeth (VIII*a*). The premature loss of these teeth results in failure of normal growth and development of the dental arches so that the permanent teeth cannot erupt properly, thus causing malocclusion (VIII*b*). The prevention of dental caries in the deciduous teeth is of great importance as damage occurring by the age of six may be irreparable.

Besides affecting the deciduous teeth, caries also occur with great frequency in permanent teeth during the first, second, and third decades (VIII*c*).

Hypoplasia of the enamel (VIII*d*), a defect in the development of the enamel of the permanent teeth, may occur in the unerupted tooth during the first year or two of life in consequence of an intercurrent infection

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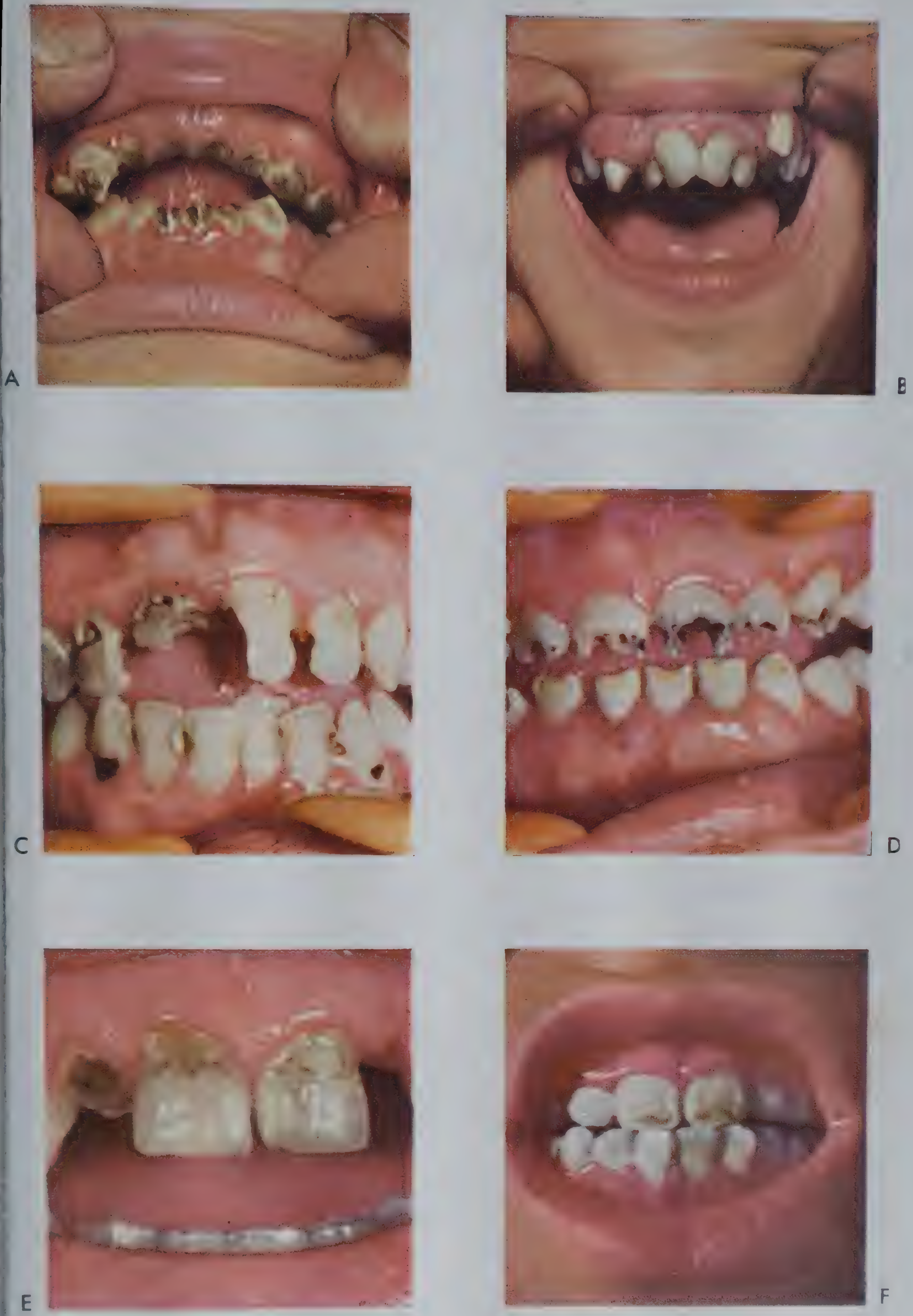
GROUP VIII.

VIII*a*. Advanced dental caries in deciduous teeth. Newfoundland.
VIII*b*. Malocclusion due to premature loss of deciduous teeth. Newfoundland.
VIII*c*. Advanced dental caries in permanent teeth. Ontario, Canada.
VIII*d*. Dental hypoplasia often associated with childbirth infections and rickets. Ontario, Canada.
VIII*e*. Dental caries showing buccal surface decalcification. New York, U.S.A.
VIII*f*. Mottled enamel (dental fluorosis) due to excess fluorine in water. Texas, U.S.A.



Group VIII

such as measles or as a result of lack of vitamin D. The defective area tends to develop in a definite line across the teeth, corresponding to the area of the enamel being formed at the time of involvement. The affected area is more subject to caries than normal areas (VIII*d*).

A type of caries called "buccal-surface caries," involving the gingival third of the tooth (VIII*e*), is often seen during the second and third decades. Many dentists report that frequently a history can be obtained that the person consumes large quantities of hard candy, holding it in the mouth until it is dissolved. While traces of fluorine tend to reduce the incidence of dental caries, soluble fluoride present in the drinking water in concentrations higher than 1 to 2 ppm produces a high incidence of "mottled enamel" (dental fluorosis) in the developing teeth (VIII*f*). Such teeth show a spotted chalky whiteness and tend to be brittle. With marked mottling, a spotted brownish discoloration also may be found, especially on the incisors.

GROUP IX: LESIONS OF THE LIPS OFTEN ASSOCIATED WITH RIBOFLAVIN DEFICIENCY

The lip lesions of riboflavin deficiency are manifested by changes in the exposed mucosa, known as cheilosis, and at the angles of the mouth, designated as angular stomatitis and dermatitis. Cheilosis manifests itself by edema, chapping, and an increase in the vertical markings, and later, when chronic, by atrophy. The edema, when present (IX*a*), is usually slight and often effaces most of the normal vertical markings. Simple desquamation (IX*b*) is the most common form of cheilosis and is usually called chapping. Slight vertical markings on the exposed mucosa of the lips may be normal, but increased vertical markings, particularly when they extend out into the surrounding skin (IX*c*), are abnormal. In atrophic cheilosis (IX*d*) the exposed mucosa becomes thin and parchment-like, and the vertical fissures disappear. This type is usually seen in older persons. Malnutrition is only one of several factors responsible for cheilosis. It may also be due to, or conditioned by, licking the lips, sun, wind, cold, chemical irritants, the wearing of braces on the incisor teeth, and allergic reactions to drugs or cosmetics.

Angular stomatitis manifests itself as a pallor, erythema, or slight maceration of the mucosa in the angles of the mouth (IX*a*) but later may spread up and down (IX*b*) for a distance of half a centimeter or more. An area of skin adjacent to the angles then becomes involved. This area of dermatitis may enlarge, following the mental folds for a distance of 2 cm. in some instances. As the lesion becomes chronic, small millimeter-sized vesicular lesions appear which later may develop into small wartlike excrescences known as pyogenic granulomata. Both the dermatitis, which follows the mental fold down onto the skin, and the granulomata represent superimposed infection. Angular fissures which are open and active are almost always in the area of angular dermatitis.

GROUP IX.

IX*a*. Acute cheilosis and angular stomatitis. Edema has effaced vertical markings. Newfoundland.

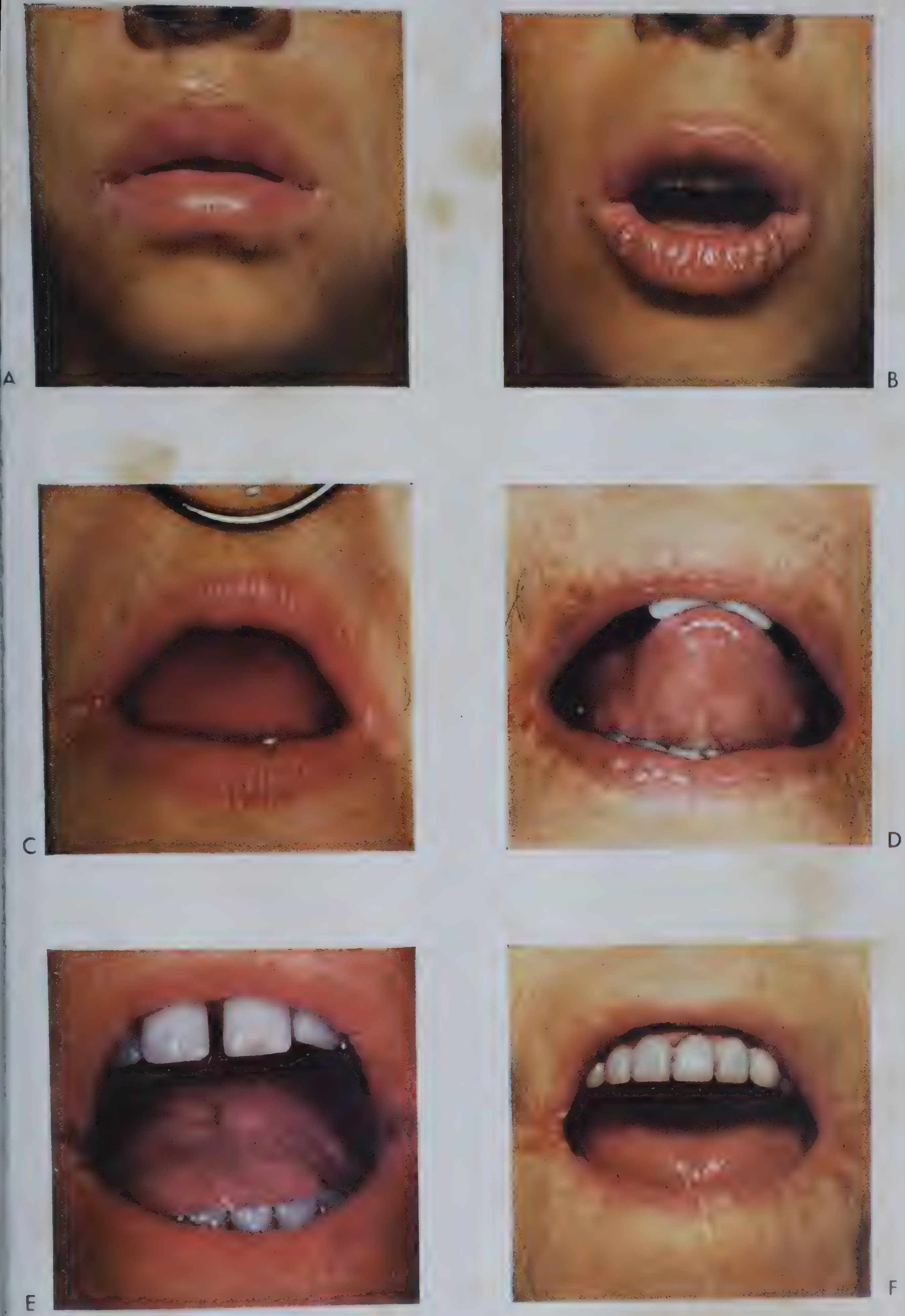
IX*b*. Chapping cheilosis and angular stomatitis: note increased vertical markings of upper lip. Newfoundland.

IX*c*. Angular stomatitis and dermatitis: note increased vertical markings. Louisiana, U.S.A.

IX*d*. Atrophic cheilosis and angular stomatitis. Aphthae of tongue incidental. New York, U.S.A.

IX*e*. Perleche superimposed on angular stomatitis. New York, U.S.A.

IX*f*. Denture cheilosis and angular dermatitis, fissures, and scars. Newfoundland.



GROUP IX

These fissures radiate from the angles and are usually bilateral but may be more marked on one side than on the other (IX*c*). When healing takes place scars often remain as evidence of old angular dermatitis.

Perleche (IX*c*) is a grayish-white lesion superimposed on angular stomatitis, dermatitis, and fissures. It may involve only the mucosa in the angles of the mouth but later extends onto the skin following the distribution of the angular dermatitis. If the lesion is cultured, many types of organisms may be found, but generally the predominant organism is the yeast *Monilia albicans.*

These lesions—angular stomatitis and dermatitis, angular fissures and perleche—are not specific of riboflavin and iron deficiencies. In infants they are often due to congenital syphilis. When they occur in children they are most often due to malnutrition and frequently respond to riboflavin administration. In adults they frequently fail to respond to iron, riboflavin, or other nutritional therapy. Most common non-nutritional factors are edentulousness, ill-fitting dentures (IX*f*), chronic drooling, and deep mental folds. It is also important to recognize that perleche may be superimposed upon angular stomatitis and dermatitis of any cause.

GROUP X: CERTAIN OCULAR LESIONS ASSOCIATED WITH MALNUTRITION

In the normal eye the area where the sclera changes to the cornea is called the limbus. At this zone the interlaced scleral fibers change to the regularly arranged corneal fibers with the scleral fibers overlying the corneal ones for a short distance. This area is referred to as the transition zone. Various layers of blood vessels traverse the sclera anastomose just before they reach the sclerocorneal junction, forming what is known as the limbic plexus. Normally, the blood vessels extend from the limbic plexus into the scleral or more superficial portion of the transition zone but not into the corneal tissue itself (X*a*). Proliferation and congestion of the blood vessels in the sclera may occur, (X*b*), particularly the limbic plexus, with extension of these vessels through the narrow transition zone into the corneal tissue. This extension occurs as a result of small vessels growing out into the cornea, anastomosing, and then sending out further twigs. A more severe degree of this extension of blood vessels into the cornea is shown in X*c*. When congestion of the blood vessels becomes extensive a pink blush appears in the circumcorneal region and is referred to as circumcorneal congestion (X*d*). This proliferation and congestion of blood vessels in the sclera and their extension into the clear corneal tissue can be produced by many causes, including, in a minority of subjects, riboflavin deficiency. Thus far, riboflavin deficiency is the only nutritional cause which has been shown to be related to these changes in man, but in the rat deficiencies of several nutrients may induce similar changes.

In man the extension of the blood vessels into the cornea is considered by many to develop most frequently in persons who have a low riboflavin intake and are also exposed to one or more conditioning factors such as bright light, smoke, dust, or other irritants.

Group X

X*a*. Normal limbic plexus of eye without extension of vessels into cornea. Royal Canadian Air Force.

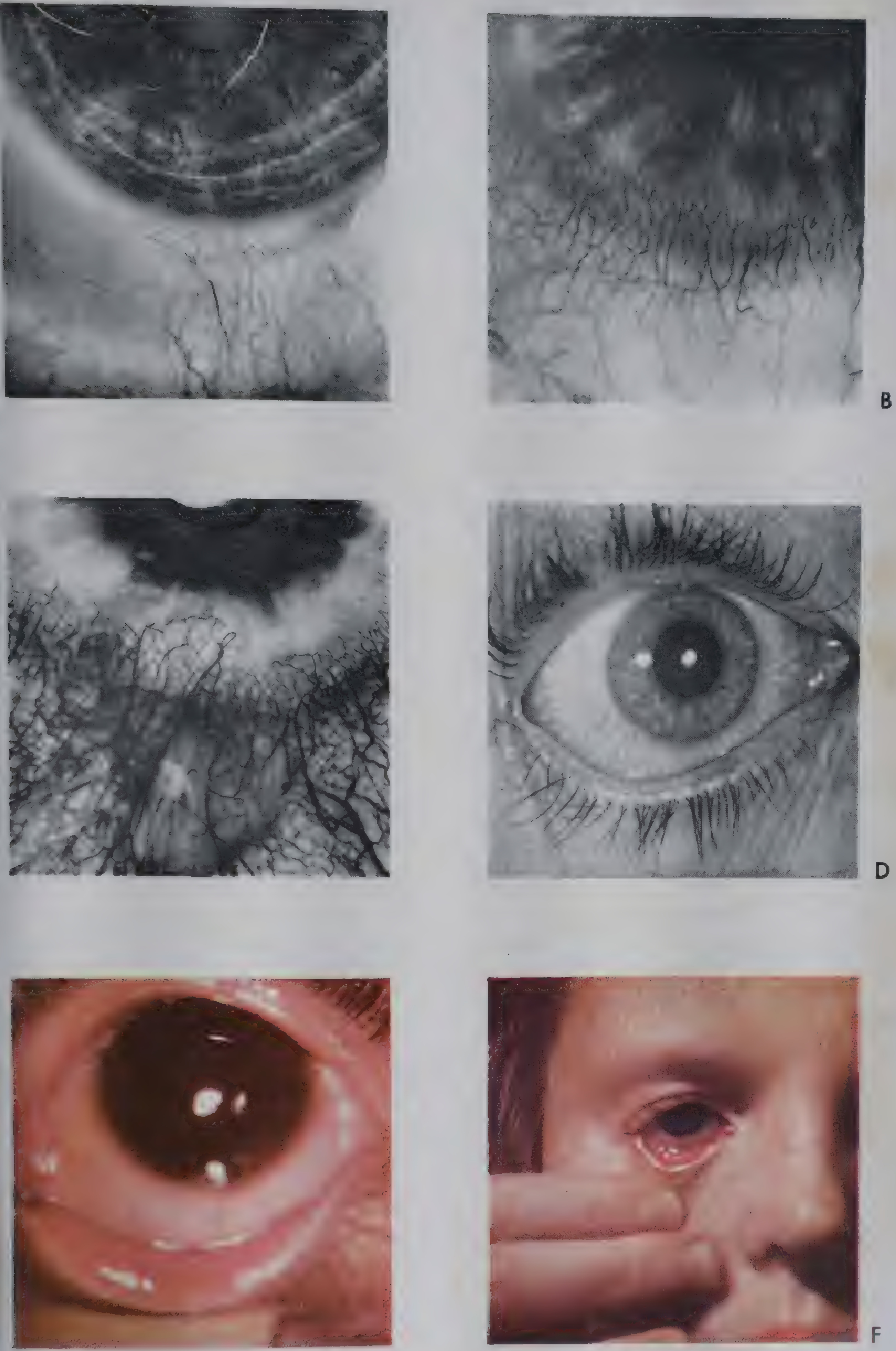
X*b*. Mild corneal vascularity showing extension into cornea. Royal Canadian Air Force.

X*c*. Moderate corneal vascularity showing greater extension into cornea. Royal Canadian Air Force.

X*d*. Circumcorneal injection showing moderate corneal vascularity. New York. U.S.A.

X*e*. Snow blindness: note hyperemia and edema of conjunctiva and clouding of cornea. Manitoba, Canada.

X*f*. Follicular hypertrophy of lower palpebral conjunctiva. Florida, U.S.A.



GROUP X

If riboflavin deficiency alone is the cause of the condition described, administration of riboflavin results in relief of the congestion and gradual emptying of the corneal blood vessels. However, examination with a slit lamp will show the outline of the empty vessels. Once these vessels have developed, from whatever cause, it is doubtful that they ever disappear completely, and it has been demonstrated that exposure to light, smoke, dust, soap, and rubbing of the eyes can cause them again to fill temporarily with blood. The condition known as snow-blindness (X*e*), which develops after prolonged exposure to glare from snow, is characterized by the same symptoms, in an exaggerated form, as those which result from riboflavin deficiency. As this condition has been relieved by the administration of riboflavin, it would appear that the combination of excessive glare and a low intake of riboflavin is an important etiologic factor.

"Granulated" eyelids or conjunctival follicular hypertrophy (X*f*) has a high incidence in malnourished children. It usually begins as a reddening and thickening of the conjunctiva of the lower lid and may progress to any stage of hypertrophy of the conjunctival follicles. In mild cases follicular hypertrophy may be seen only on the lateral aspect of the lower lid, the upper lid showing no lesions. In cases with well-developed lesions the hypertrophied follicles appear to be granular elevations which are punctate and discrete, resembling sand on the conjunctiva. Usually there is little inflammation (X*f*).

This condition must be differentiated from trachoma, with its marked inflammatory reaction, its typical granular appearance, and, usually, involvement of the upper lid first. Trachoma also involves the bulbar conjunctiva and cornea and causes scarring of the palpebral conjunctivae. Vernal catarrh presents a cobblestone type of the follicular hypertrophy, with a flat surface and an adherent milky white pseudomembrane. It is seasonal and recurrent, with a tendency to cease (self-cure) following adolescence.

GROUP XI: FREQUENT FINDINGS IN BERIBERI

Beriberi is a clinical syndrome characterized by neuropsychiatric, circulatory, gastrointestinal, and metabolic disturbances caused by thiamine deficiency. It is frequently complicated by other nutritional deficiencies and other diseases.

The objective signs are often preceded by anorexia, fatigability, apathy, digestive symptoms (which in acute cases may consist of nausea and vomiting), and disturbances in the sleep pattern. Added to these may be heart consciousness, paresthesias, inability to concentrate, and a feeling of despair. These neurasthenic symptoms are of course nonspecific, but they frequently precede the development of both endemic and experimental beriberi as well as pellagra and mixed deficiency syndromes. The earliest objective signs are plantar dysesthesia, calf-muscle tenderness, and weakness of the quadriceps muscles making it difficult to arise from the squatting position. Then the vibratory sensation in the toes becomes diminished, the knee jerks become more active, and the ankle jerks are lost. Later the plantar dysesthesia extends up the leg and vibratory sensation is diminished in the malleolus or even in the tibia. Errors may be made in the detection of small changes in the position of the toes, and soon the knee jerks diminish and later cannot be obtained. Some atrophy of the calf muscles may now be present; foot and toe drop and steppage gait also may become evident (XI*a*). Atrophy of the thigh and leg muscles may become severe, and still later the upper extremities become affected in a similar manner. Central scotoma may occur which may cause permanent loss of macular vision.

At any time during the course of the polyneuropathy, and sometimes independently of it, circulatory disturbances may develop, especially during hot weather and in those who continue to work. These disturbances consist most commonly of edema (the so-called wet beriberi, XI*b*) with or without serous effusions, congestive heart failure, and sudden circulatory collapse.

Edema without enlargement of the heart or other signs of congestive

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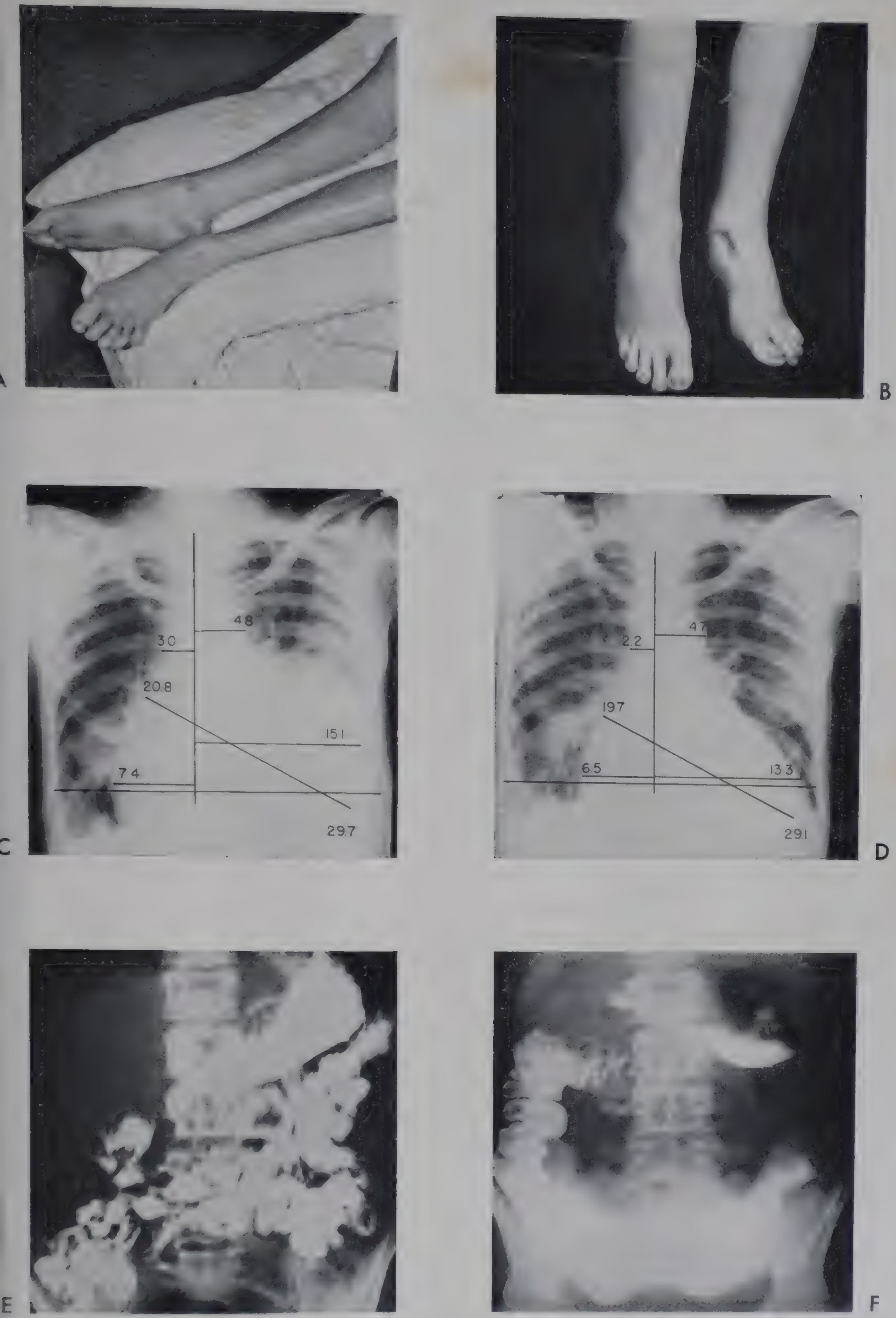
GROUP XI.

XI*a*. Advanced polyneuropathy with muscle atrophy, foot and toe drop. New York, U.S.A.
XI*b*. Edema in a patient with beriberi. Alabama, U.S.A.
XI*c*. Beriberi heart, showing enlargement in all diameters. New York, U.S.A.
XI*d*. Beriberi heart after treatment. New York, U.S.A.
XI*e*. Delayed emptying time and lack of tone of gastrointestinal tract in thiamine deficiency. Minnesota, U.S.A.
XI*f*. Same person after treatment. Minnesota, U.S.A.


A
B
3.0
4.8
20.8
15.1
7.4
29.7
C
2.2
4.7
19.7
6.5
13.3
29.1
D
E
F

Group XI

failure is probably the most frequent type of circulatory disturbance. It may range from mild edema to anasarca and may or may not be associated with low plasma proteins. With normal plasma proteins the response to rest is often dramatic.

Although the congestive failure may involve both sides of the heart, right sided failure often predominates. It may be of any degree of severity, and a "red" cyanosis due to arteriolar dilatation is common. The pulse is rapid and often there is a high pulse pressure with audible arterial sounds over the brachial artery at the elbow. Radiographic examination shows generalized enlargement (XI*c*) of the heart in all diameters except when enlargement of the right side predominates. After therapy the size of the heart decreases toward normal (XI*d*). Electrocardiographic tracings usually disclose some abnormalities but none that is diagnostic. Heart failure of this type often makes a dramatic response to thiamine.

Circulatory collapse and sudden death, usually associated with effort, are described as common in most studies of beriberi in the Orient. This condition may resemble shock or the syndrome produced by a hyperactive carotid sinus reflex of the vagotonic type. Circulatory collapse may occur either without previous warning or only after other circulatory disturbances are well established.

The most common gastrointestinal X-ray finding is a delay in passage of the barium meal through the small intestine (XI*e* and *f*) with other evidences of a lack of intestinal tone.

GROUP XII: ROENTGENOGRAPHIC FINDINGS IN RICKETS, SCURVY, AND OSTEOMALACIA

In many parts of the world the common bony lesion of active rickets is found on roentgenographic examination of infants. The characteristic roentgenographic changes which develop rapidly often become visible by roentgenogram in the third or fourth and occasionally even in the second month and precede the clinical manifestations of the disease. Occasionally, if the mother has osteomalacia, the roentgenographic signs of rickets are already visible at birth (fetal rickets). The changes are most easily detected at the lower ends of the radius and ulna. The ends lose their sharp linear outline, show rarefaction which is often spotty or fringing, and become broadened or actually cup-shaped (XII*b*). If rickets proceeds, the distance between the ends of the radius and ulna and the metacarpal bones appears increased because the true ends are invisible as the result of the failure of calcification. At the same time the shadows cast by the shafts decrease in density and the network formed by their interlacing laminae coarsens. The failure in the deposition of calcium so weakens the bone that it bends at the cartilage-shaft junctions or in the substance of the shafts, with the production of characteristic deformities (XII*b* and *c*).

Administration of vitamin D in the form of fish liver oil, irradiated 7-dehydrocholesterol (vitamin D_3) or irradiated ergosterol (vitamin D_2), and direct exposure of the skin to ultraviolet rays derived from the sun or the ultraviolet lamp will prevent the development of these changes or, if they have already developed, will restore normal bone formation.

In contrast to rickets, the roentgenographic changes characteristic of scurvy occur only in the presence of clinical signs. The ends of the long bones have a more dense appearance than is normal, giving the characteristic "white line" of scurvy (XII*c*). On the shaftward side of the "white

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GROUP XII.

XII*a*. Normal bones of infant aged 8 months, for comparison. Ontario, Canada.
XII*b*. Active rickets in infant aged 7 months. Ends irregular and broadened with rarefaction of bone. Ontario, Canada.
XII*c*. Active scurvy in infant aged 7 months. Subperiosteal hemorrhage not visible. Ontario, Canada.
XII*d*. Active scurvy after treatment for fourteen days. Calcification makes elevated periosteum visible. Note displacement of epiphysis. Ontario, Canada.
XII*e*. Normal pelvis of woman aged 21, for comparison. Illinois, U.S.A.
XII*f*. Osteomalacia of woman aged 28. Note deformity and rarefaction. Illinois, U.S.A.

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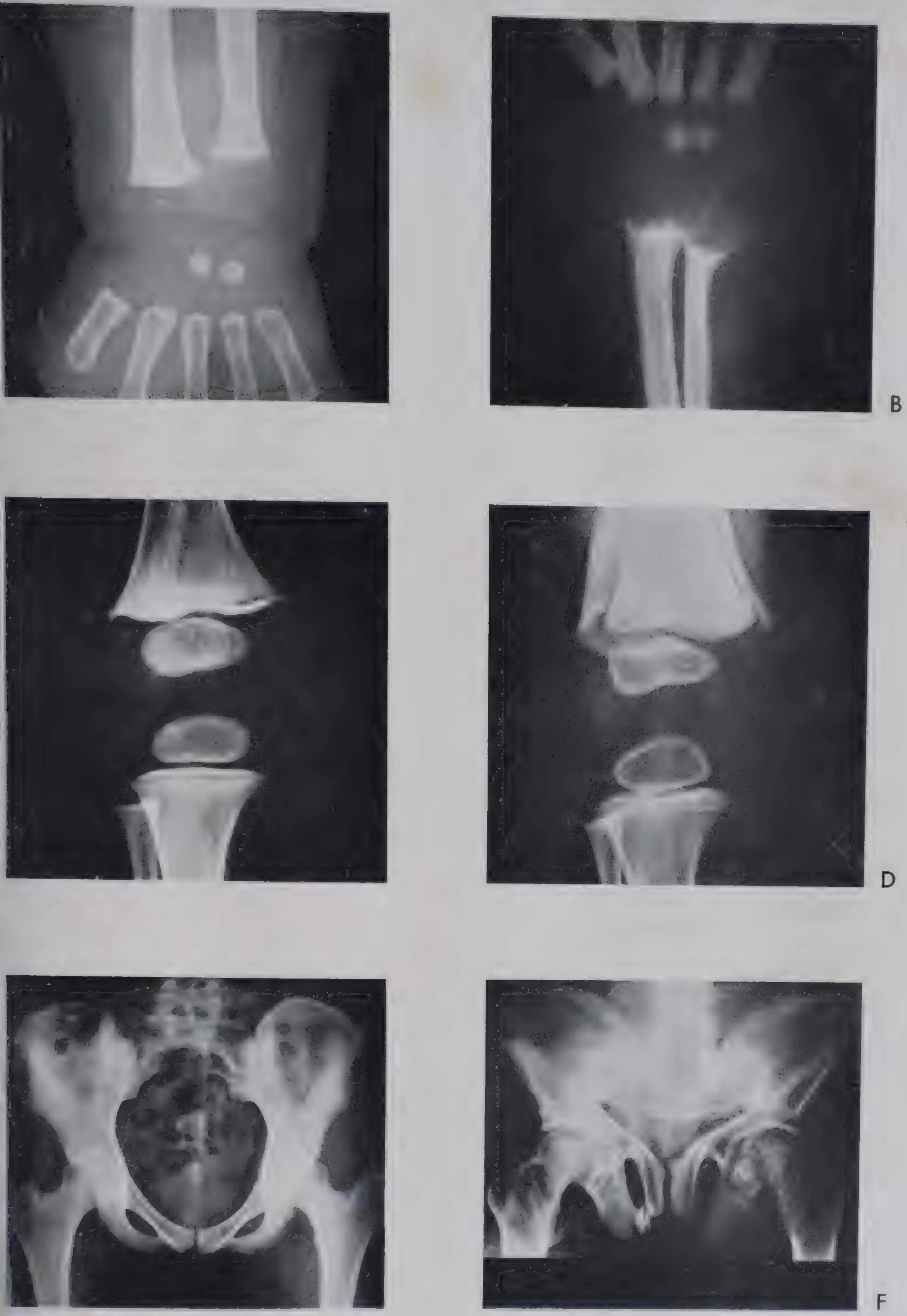

Group XII

line" there is rarefaction. The earliest lesions visible on the X-ray which are pathognomonic of scurvy are minute fractures situated at the "corners" of the ends of the bones, particularly well seen at the lower ends of the radius and ulna and tibia. These fractures appear often as clefts if pulling apart has occurred, or as extrusions if the fractured parts have been compressed and fragments squeezed outward. If the disease has reached a severe stage, these fractures extend completely across the end of the bone. The shafts, as a result of rarefaction, have a "ground glass" appearance which is not, however, peculiar to scurvy. In severe subperiosteal hemorrhage wide separation of the periosteum is frequent. This lesion does not become visible in the X-ray film, except as swelling of the soft parts, until a week or more after treatment with vitamin C (XII*d*) when, for the first time, the displaced periosteum becomes calcified and visible. The subperiosteal hemorrhages always result from fractures of the shaft close to the epiphysis. These fractures often result in wide displacement of the epiphyses which may be detected by noting that the centers of ossification of the epiphyses are to one side of the line of the shaft (XII*e*).

Osteomalacia (XII*f*) is the adult counterpart of rickets in the infant. It is common in the Orient but rare in the Occident and is usually seen only in extreme food faddism, starvation or failure of absorption, and chronic diarrheal diseases. The bones, particularly those of the spine, pelvis, and lower extremities, become decalcified so that the fibrous lamellae become visible on the roentgenogram. At the same time incomplete fissure-like fractures appear in the cortex of the bone. These were formerly called "proliferation zones." As the bones soften, forces of weight-bearing push on the pelvis from above and below, causing deformities which alter the pelvic outlet. Recalcification occurs after treatment with vitamin D and calcium but the deformities remain to constitute a hazard in childbirth.

GROUP XIII: STARVATION

Starvation is a severe degree of caloric undernutrition; it is usually complicated by one or more factors of shelter, sanitation, emotion, quality of the diet, and disease. Acute fasting and lifelong undernutrition represent two extremes; the present section refers primarily to the common conditions associated with famine, anorexia nervosa, and a variety of disease states. The primary characteristics are emaciation and loss of weight or marked deficiency of weight in relation to height (or to age in children), but these may be somewhat masked by edema. Emaciation of the upper trunk and arms, with winged scapulae, prominent zygomatic arch, and sagging buttocks, is universal (XIII, *a*, *b*, *c*, and *d*).

The general appearance and behavior is that of apathy, depression, chronic illness, and weakness. The face is pallid, the skin is thin, cold to the touch, dry, rough, and inelastic. The nailbeds are slightly cyanotic and some cyanosis may appear in the lips and over the cheekbones in cold weather. Irregular areas of a dirty brown pigmentation of the skin appear in many cases (XIII*c* and *d*). The eyes appear dull and the sclerae resemble unglazed porcelain. The hair is dull and "staring." The lips are dry and frequently cracked or peeling. The tongue shows no specific abnormalities but marked dental impressions often reveal lingual edema. Slight to moderate peripheral edema is common. The pulse is weak, regular, and very slow at rest; in exercise the acceleration is relatively moderate except in the presence of such complications as infections or beriberi.

On detailed examination the muscle tone is poor and the tendon reflexes are frequently diminished and occasionally absent, but paresthesias are uncommon. The blood pressure is low (100 or less, systolic), with a distinctly narrow pulse pressure. The electrocardiogram shows low voltage in all waves with relatively normal PR and QRS intervals; there is a tendency toward right axis deviation. The venous pressure is reduced. Roentgenographic examination shows that the heart is small, (XIII*e* and

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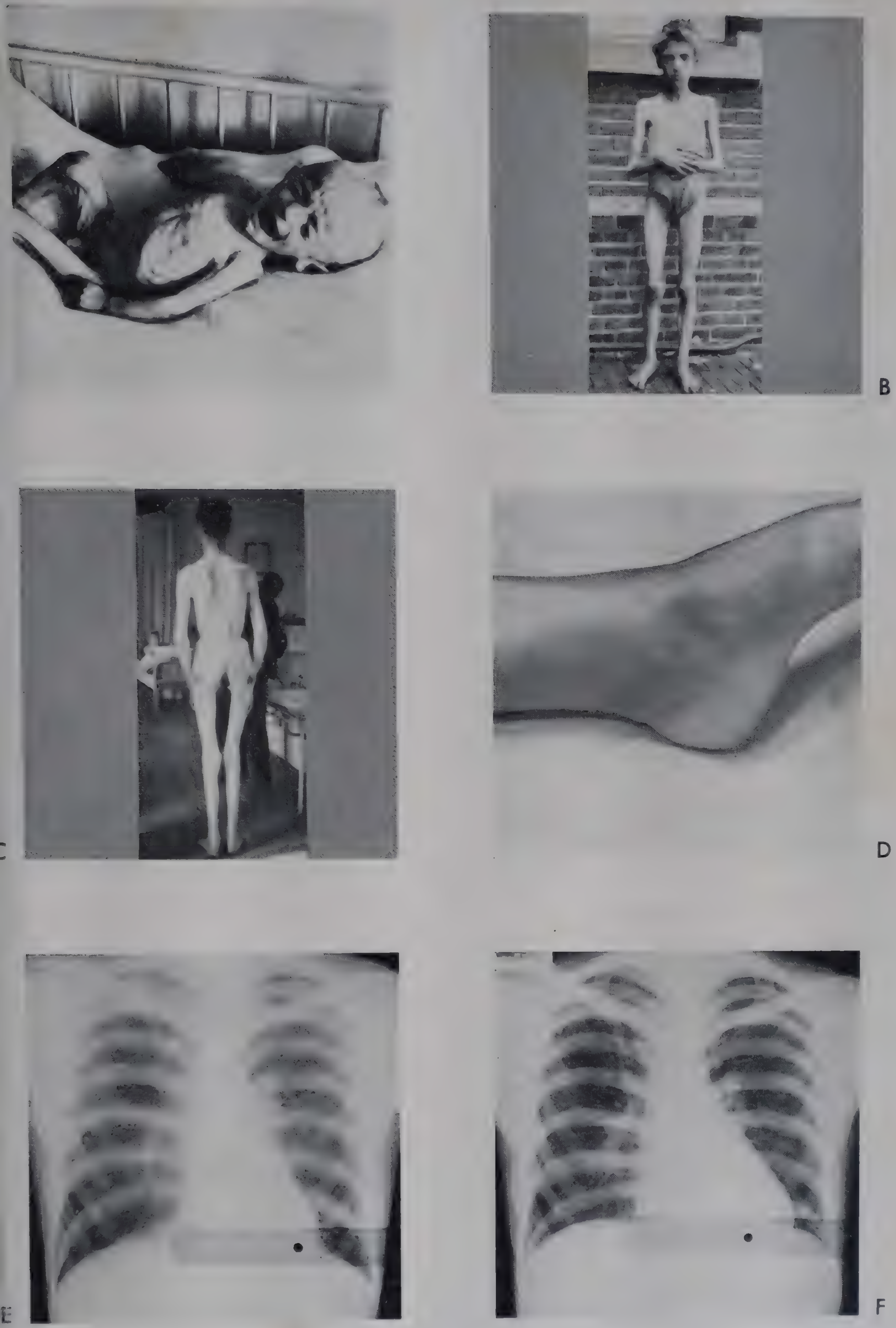
Group XIII.

XIII*a*. Emaciation, flexion of legs and enophthalmos. Germany.
XIII*b*. Starvation in young adult female: emaciation, stunting, and loss of secondary sex characteristics. Netherlands.
XIII*c*. Starvation in young adult male: emaciation and pressure point pigmentation. Netherlands.
XIII*d*. Starvation in adult female: pigmentation and hunger edema. New Jersey, U.S.A.
VIII*e*. Atrophy of heart in starvation. Germany.
XIII*f*. Same patient after 6 weeks of feeding. Germany.



GROUP XIII

f) and the lungs usually clear. The body temperature is subnormal and the basal metabolic rate between minus 10 and minus 40. Anemia and hypoproteinemia are moderate, severe degrees of these being associated with the complications of infections, infestations, or extreme protein deficiency. The anemia is usually macrocytic; the white blood-cell picture is not specific but there is a tendency toward leukopenia. The blood sugar level is low, while the lactic and pyruvic acid levels are slightly elevated. The urine is voluminous, dilute, and protein-free. In the female there is marked atrophy of the breasts (XIII*b*) and vulva; amenorrhea is almost universal. In the male the penis is flaccid and shrunken and the testicles are small.

In the terminal stages edema (XIII*d*) may disappear and cardiac irregularities may be observed. The patient lies motionless with legs drawn up, (XIII*a*) unresponsive to ordinary stimuli but giving signs of objection to being moved. Death may come suddenly but more often there is first a prolonged shocklike state where vigilance is needed to detect life.

On refeeding, edema may come and go and there is a marked tendency to lay down fat instead of more vital tissues, so that in this stage the extent of disability is difficult to gauge from either weight or superficial appearance. The basal metabolic rate rises to normal or above and there may be relative tachycardia both at rest and upon exercising. The scaphoid abdomen changes to become protuberant. Transient hypertension is not uncommon. Anemia and poor muscle tone are relatively persistent.

The most important complications are those associated with poor sanitation and with recourse to foods which are coarse, bulky, and poor in vitamins and proteins. Faulty personal hygiene is reflected in a high incidence of minor skin infections. Coarse, bulky foods, often more or less spoiled, seem to be at least partly responsible for the great frequency of diarrhea in famine victims; in many of these cases specific pathogens are not found in the stools. The complicating effects of extreme deficiency of vitamins and proteins are most often seen in the Orient. Under these conditions it is not uncommon to find amblyopia, severe paresthesias of the extremities, ascites, and other signs which are not dependent on caloric deficiency alone. In the presence of severe emaciation it is advisable to look for other factors in addition to caloric want if one or more of the following signs are observed: Extreme anemia, ascites and marked general edema, definite cutaneous anesthesia or hyperesthesia, purulent diarrhea, amblyopia, vomiting, tachycardia (however slight), leukocytosis, albuminous urine, dyspnea at rest, and a body temperature above 98.0° F.

GROUP XIV: LESIONS FREQUENTLY SEEN IN MALNOURISHED PERSONS

There are certain lesions of doubtful etiology which occur so frequently in ill-nourished persons that it is reasonable to suspect they may be caused by malnutrition. Among these lesions are "spider" telangiectasis, palmar erythema, marginal blepharitis, suborbital pigmentation, and thickening of the conjunctivae.

"Spider" telangiectasis (XIV*a*) consists of a bright-red millimeter-sized dilated capillary as the central body from which radiate threadlike branches for a distance of up to two or more centimeters. The lesions are most common on the face and near the clavicle but may occur anywhere above the umbilicus, including the nasal septum, lips, tongue, and conjunctivae.

Palmar erythema, or "liver" palms (XIV*b*), is a symmetrical capillary and arteriolar dilatation involving the eminences of the palms and digits of the hands and sometimes the soles. It occasionally extends over the fingertips to the nailbeds and lateral parts of the distal phalanges. As a rule there is a triangular area in the center of the palm, with the apex toward the wrists, which is spared. The increased color disappears on pressure but does not fade on elevation of the hand.

Both "spider" telangiectasis and palmar erythema occur in a number of diseases. They are frequently found in patients with liver disease. When observed during pregnancy or in persons seemingly healthy, they should arouse a suspicion of malnutrition.

Marginal blepharitis may consist of a simple hyperemia, differing from that caused by weeping or exposure in that it is persistent.

This is followed by small, white, dandruff-like scales (XIV*c*) which accumulate among the lashes. When these scales are removed the underlying surface is found to be reddened or slightly hyperemic but not ulcerated. The lashes may fall out easily but grow back without distortion.

GROUP XIV.

XIV*a*. Spider telangiectasis in a person with liver disease. New York, U.S.A.

XIV*b*. Palmar erythema or "liver" palms in a person with multiple deficiency disease, New Jersey, U.S.A.

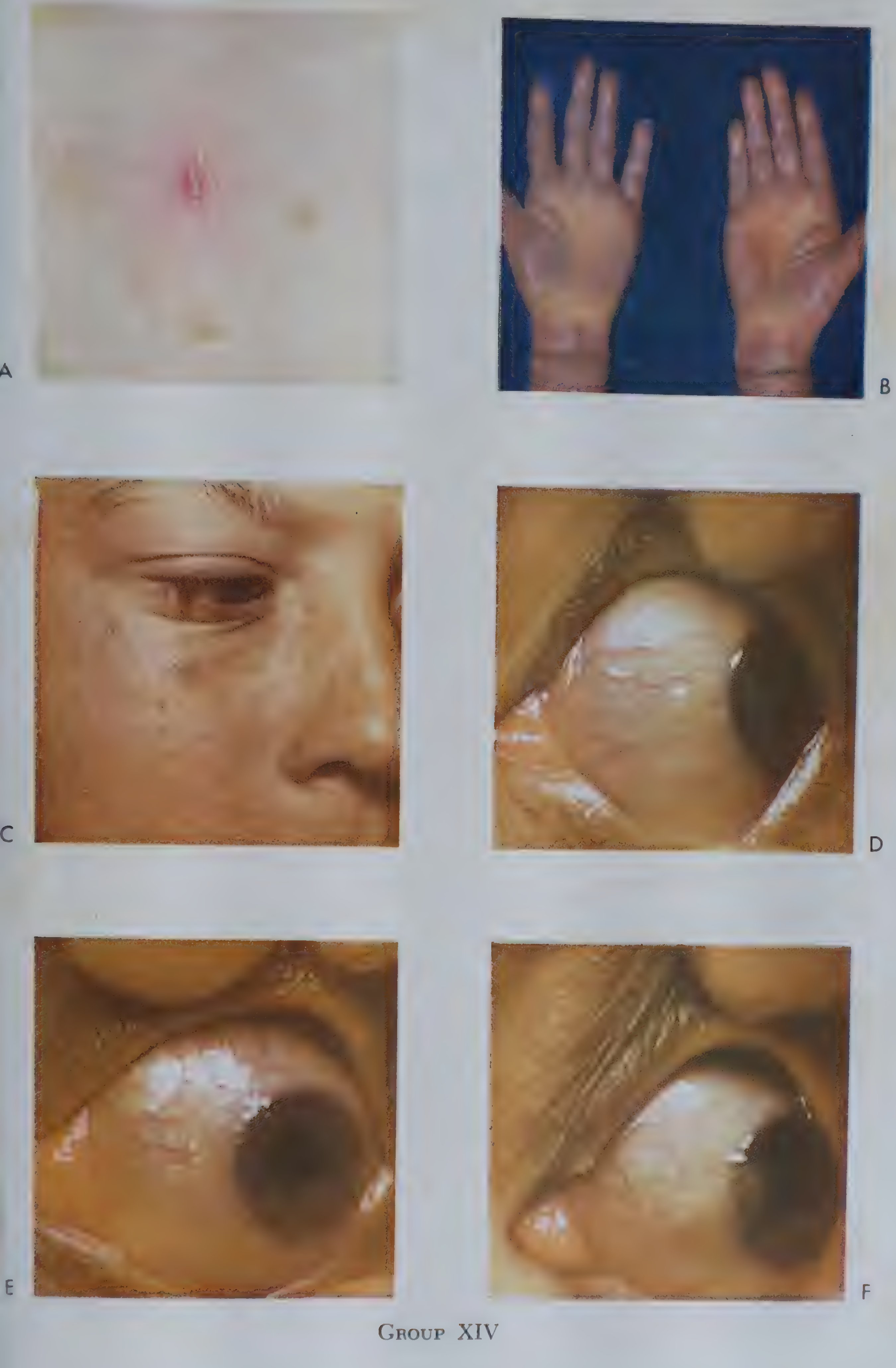
XIV*c*. Suborbital pigmentation and blepharitis. Newfoundland.

*XIV*d*. Thickening of conjunctiva. Manitoba, Canada.

* XIV*e*. Thickening of conjunctivae with triangular shaped elevation. Manitoba, Canada.

* XIV*f*. Pterygium. Manitoba, Canada.

* The brown tone of the skin and eyes of the Indians has been somewhat exaggerated in these illustrations.



GROUP XIV

This lesion is often associated with dyssebacic cutaneous lesions and ocular symptoms suggestive of riboflavin deficiency, or with follicular hyperkeratosis and xerosis of the skin, and is extremely common in malnourished population groups.

Suborbital pigmentation (XIV*c*) is a patchy distribution of brown pigment below the eyes, usually in a roughly triangular shape, and is frequently observed in malnourished children. It is to be distinguished from the circular eye shadows frequently observed after loss of sleep.

Thickening of the conjunctivae occurs with considerable frequency, however, in population groups who are malnourished. Some investigators believe that the thickening of the conjunctivae is due to a vitamin A deficiency. Normally the bulbar conjunctiva is bluish-white, smooth, and transparent, with the subconjunctival vascular network readily visible. As thickening develops, the transparency of the conjunctiva is replaced by a ground-glass-like translucency, often with yellowish pigment. Small areas, most commonly on the nasal side of the limbus, become heaped up, uneven, creamy yellow or brown (XIV*d*). The deeper vascular network becomes invisible because of conjunctival opacity. As the small areas enlarge they become more prominent and often triangular with the base toward the limbus (XIV*c*), although other forms are frequently noted. To be distinguished from the thickening of the conjunctiva just described is the pterygium (XIV*f*) which grows from the conjunctiva, usually from the nasal side, over the cornea, sometimes extending to the center of the pupil. A nutritional factor has not been claimed for pterygium. Both these lesions are particularly common in the Indians and Eskimos of the subarctic regions of North America.

GROUP XV: MISCELLANEOUS NUTRITIONAL LESIONS

One of the signs of infantile scurvy is the scorbutic rosary (XV*a*). It is characterized by a sharp angular enlargement at the junction of the cartilage with the rib. The sternum and costal cartilages give the impression of having been pushed back so that a sharp angle is produced at the costochondral junctions. In contrast, the costochondral junctions in the rachitic rosary (XV*b*) are rounded.

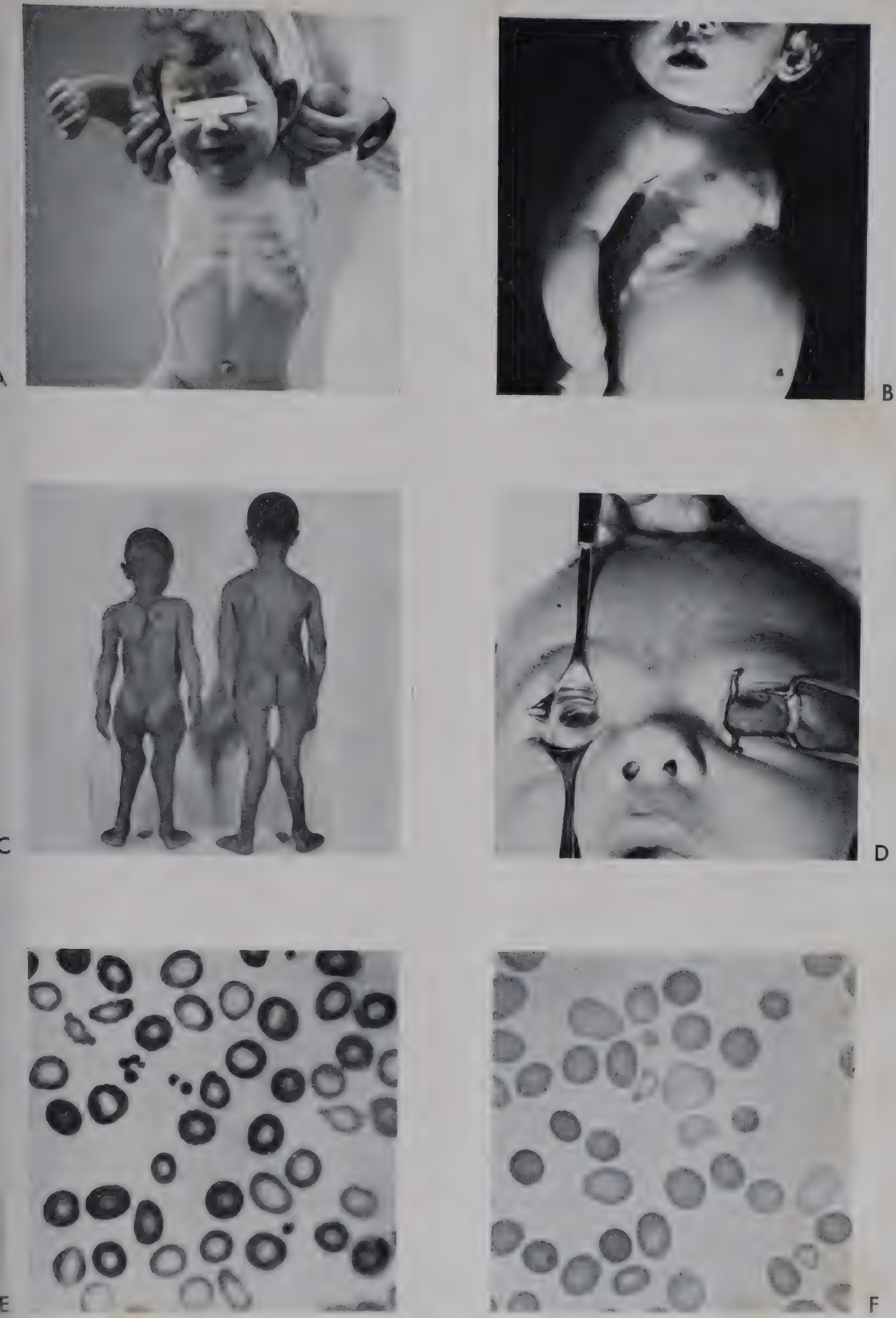
Some of the other bony deformities characteristic of advanced rickets are shown in XV*c*. The long bones frequently are curved and shortened, producing either knock knees or bowlegs. Enlargement of the epiphyses of the long bones at the wrists and ankles can be seen. Deformity of the pelvis in both the children in the illustration is apparent. Such deformity in the female may interfere with childbirth. These deformities when seen in older children are usually the result of rickets in early life and do not indicate that the disease is active.

Keratomalacia results from severe deficiency of vitamin A over a period of some months (XV*d*). The patient here illustrated received no carotene or vitamin A in her food or by supplement for five months. The corneas appear hazy and dry. The conjunctivae are dry, wrinkled, and injected. Some fatty-looking deposits are on the conjunctivae. On the left cornea there is an area of beginning ulceration. Keratomalacia is common in the Orient, where it is a frequent cause of blindness.

Nutritional anemias rank among the more common clinically evident nutritional diseases in the world today. They include both the hypochromic and the hyperchromic types. The most common of the nutritional hypochromic anemias is that due to iron deficiency, an anemia characterized by a low serum iron and by response to iron therapy. At the height of the anemia the red cells are reduced proportionately less than the hemoglobin, giving a low color and volume index. The blood smear characteristically shows a predominant microcytosis, hypochromia, and poikilocytosis (XV*e*).

GROUP XV.

XV*a*. Scorbutic rosary. New York, U.S.A.
XV*b*. Rachitic rosary. Massachusetts, U.S.A.
XV*c*. Rachitic deformities. Maryland, U.S.A.
XV*d*. Keratomalacia. Note the dry wrinkles, injected conjunctivae and cloudy corneas. Ontario, Canada.
XV*e*. Hypochromic anemia. Note the microcytosis, hypochromia and numerous platelets. Responded later to iron. Toronto, Canada.
XV*f*. Hyperchromic anemia. Note the macrocytosis, polychromatophilia and poikilocytosis. Responded later to folic acid. New York, U.S.A.



Group XV

Nutritional hyperchromic anemias include the macrocytic anemias of addisonian pernicious anemia and of the tropics, those seen in sprue, gestation, pellagra, and malnutrition, and the gastroenteric and megaloblastic juvenile anemias. Liver extract is therapeutically effective in all these varieties, but their definite classification in the field of deficiency diseases was possible only after folic acid was synthesized and found to be therapeutically effective. Though there are minor differences in the blood smears, all forms of hyperchromic anemia in relapse show characteristically a predominant macrocytosis with bizarre shapes, polychromatophilia, and nuclear remnants (XV*f*). The red cells are reduced proportionally more than the hemoglobin, giving a high color and volume index. Addisonian pernicious anemia is distinguished from other macrocytic anemias by a histamine-fast achlorhydria, higher color and volume index, a more severe grade of anemia, leukopenia, and, often, severe neurologic involvement. Folic acid seems to be effective in macrocytic anemias showing megaloblasts with erythroblastic arrest in bone marrow, but apparently is ineffective for the prevention and relief of spinal tract degeneration. Vitamin B_{12} apparently will prevent spinal tract degeneration in addisonian pernicious anemia and relieve in this disease the acute neurologic changes.

NOTE

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Chapter 4

BIOCHEMICAL METHODS

Grace A. Goldsmith

As information has accumulated concerning the chemical structure and function of essential nutritive factors, procedures have been developed for measuring the levels of these substances in bodily tissues and fluids, and for detecting metabolic abnormalities which occur when the supply of these nutrients is insufficient.

Specific nutrients which have been studied in nutritional surveys with the use of biochemical methods include protein, iron, calcium, vitamin A, thiamine, riboflavin, niacin, ascorbic acid, vitamin D, and occasionally certain other substances. Each of these nutrients will be considered individually, existing methods of determination appraised, and the interpretation of findings discussed.

PROTEIN

In the evaluation of protein nutrition in population groups, the only chemical test which has been widely applied has been the determination of total serum or plasma protein, although the albumin and globulin fractions have also been measured in a few instances. In early studies, serum proteins were estimated by either the macro- or micro-Kjeldahl

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technics. With the latter procedure, either titration or nesslerization has been used in estimating total nitrogen. More recently, methods dependent on specific gravity have been devised. These have the advantage of speed and simplicity while retaining a high degree of accuracy. The falling drop method of Barbour and Hamilton[9] or of Kagan,[97] the copper sulphate method of Phillips, Van Slyke *et al.*[177] and the micro method of Lowry and Hunter[123] using the Linderstrom Lang gradient tube, are all satisfactory. Atchley[6] found excellent agreement between the falling drop and copper sulphate methods and reasonably good checks between findings with these procedures and micro-Kjeldahl determinations. The standard procedure for determining serum albumin has been separation from globulin by salt precipitation[179-181] or the sodium sulphate method[31] followed by determination of nitrogen by the Kjeldahl technic. Recently Lerner and Barnum[117] have proposed a method for the estimation of serum albumin and globulin based on determination of the ultraviolet absorption of a diluted solution of serum proteins in a spectrophotometer. Total protein is measured simultaneously by one of the rapid specific gravity methods and serum albumin calculated from the combined data. This procedure may be applicable to surveys and appears worthy of critical testing.

The normal range for total serum protein in adults has been stated to be 6 to 8 Gm. per 100 cc.; for serum albumin 4.0 to 5.5 Gm. per 100 cc.[174] The level of total serum protein is not as significant as that of albumin in evaluating protein nutrition since it is influenced by the globulin fraction which may be increased in a number of pathologic states. In a recent study of 1100 subjects Youmans *et al.*[218] found that 89 per cent of those with hypoalbuminemia had a normal concentration of total serum proteins.

Hypoproteinemia occurs when the protein in the diet is severely curtailed for long periods of time and in a number of diseases, including those involving the liver, certain types of renal pathology, and many conditions associated with loss of protein from the body.

The concentration of plasma proteins may remain constant for long periods of time in the presence of dietary protein deficiency. This may be due in part to the masking effect of hemoconcentration.[138] If the volume of circulating plasma is determined, protein depletion may be detected at an earlier stage. The experiments of Madden, Whipple, and associates[128] have shown that plasma protein reflects tissue stores. Sachar and coworkers[186] have calculated that a reduction of 1 Gm. in the total circulating plasma albumin indicates a loss of 30 Gm. of body protein. A reduction in plasma albumin concentration from 4 to 3.5 Gm. per 100 cc., in a person whose plasma volume was 3500 cc., would mean a reduction in total plasma albumin of 17 Gm. and a tissue loss of about 510 Gm.[201] If Sachar's findings are correct, hypoproteinemia indicates protein deficiency of moderately advanced degree. Slight reduction in the concentration of total serum protein, or particularly of serum albumin, is significant in persons who are ambulatory and without signs of complicating disease.

In nutrition surveys in the United States[144, 218] hypoproteinemia has been an uncommon finding. In the study of a large population group in Tennessee, the incidence of hypoproteinemia was 3 per cent, of hypoalbuminemia 9 per cent.[218] There was no demonstrable correlation between the level of serum albumin and the intake of calories, total protein, or animal protein. Dietary restrictions must apparently be more severe than those encountered in this study before a relationship between serum levels and protein intake can be demonstrated.

In a study of protein requirements, Hegsted and coworkers[72] found that total protein, plasma albumin, and plasma globulin tended to decrease when low protein, all-vegetable diets were fed at a level low enough to produce negative nitrogen balance. Kark, Bean, and their coworkers[99] in a study of the nutrition of troops in tropical areas found that there was reasonable correlation between the average intake of protein and the concentration in the serum. Indian troops, with a lower intake than Americans or Canadians, had lower levels of serum protein. Hypoproteinemia of mild degree was found to be common in certain famine areas[102] and in concentration camps[120] in the Second World War. Keys and coworkers[102] found a slight decrease in the plasma protein in 34 men maintained on a European type of famine diet for six months. A close correlation between "hunger" edema and levels of serum protein was not observed in these studies or in similar investigations elsewhere. This is not surprising in view of the multiple factors which affect edema formation. The complete story of the pathogenesis of nutritional edema has not been elucidated.

In the light of available evidence, it seems fair to interpret a low concentration of protein in the blood, particularly of the albumin fraction, as indicative of dietary protein deficiency if disease etiologically associated with low levels of serum protein can be eliminated.

IRON AND HEMOGLOBIN

One of the most widely used methods in appraisal of nutritional status is the determination of hemoglobin in the blood. The mean level of hemoglobin and the percentage of persons with values below the accepted range of normal have been considered good indices of the general health of the population. Many adverse environmental conditions, numerous pathologic states, particularly infections and diseases associated with blood loss, and several dietary factors, are important in the production of anemia. The quantity of hemoglobin in the blood has often been used as a measure of the prevalence of iron deficiency. This is not justifiable unless improvement can be demonstrated following therapy with iron. Iron deficiency is the most common dietary factor leading to anemia, but deficiency of protein, folic acid and other less well defined nutrients such as the "extrinsic" factor, may be of etiologic importance.

There are many methods for the determination of hemoglobin, none of which is ideal. Hemoglobin may be determined by dilution of blood with water[51] to which ammonia may be added to increase the stability of the oxyhemoglobin.[214] Bessey and Lowry[15] developed a micro method requiring only 10 cu. mm. of whole blood in which, following dilution, hemoglobin is measured by light absorption in the photoelectric colorimeter.

Acid hematin procedures, although widely used, are largely unsatisfactory. It is difficult to obtain an accurate standard and color is affected by nonhemoglobin substances.[214] The cyanmethemoglobin method is simple and accurate but the hazard of cyanide precludes its routine use.[104] The alkaline hematin and carboxyhemoglobin procedures are a little less accurate but are satisfactory for most purposes.[104] The alkaline hematin method is preferable because it estimates carboxyhemoglobin, methemoglobin, and sulfhemoglobin in addition to active hemoglobin. Regardless of the method chosen, photoelectric instruments are preferable to the older visual colorimeters for measurement of intensity of color. All instruments should be calibrated with one of several accurate methods such as: (1) determination of oxygen capacity;[175] (2) estimation of the iron content of blood or erythrocytes with the titanous chloride procedure;[104] (3) the pyridine hemochromogen method with crystalline hemin as a standard;[214] or (4) crystalline hemin in N/10 borate buffer at *p*H 9.4.[81]

Determination of hemoglobin indirectly from the specific gravity of whole blood and plasma, with the copper sulphate procedure of Phillips, Van Slyke, *et al.*[177] has been used in many recent surveys. An accuracy of ±2 per cent is claimed for this method.

An anemia due to iron deficiency can usually be differentiated from anemia of other causation by determination of the volume of packed erythrocytes (hematocrit) and estimation of the red cell count. From these data the size of the cells (mean corpuscular volume), and the mean corpuscular hemoglobin concentration can be calculated. Iron deficiency anemia is hypochromic and often microcytic. Mean corpuscular hemoglobin concentration falls below the normal of 34 ± 2 per cent while mean corpuscular volume is often less than the normal of 87 ± 5 cu. micra.

The anemia of folic acid deficiency, sprue, pernicious anemia, and possibly of protein deficiency is macrocytic and the mean corpuscular volume is high.

Determination of the erythrocyte count with the usual counting chamber method is not feasible in surveys. Recently, however, Blum[20] has developed a photoelectric method for estimating the red cell count which may be applicable to mass studies. Hematocrit determination is relatively easy to perform. In future surveys, it should be possible to estimate mean corpuscular volume and mean corpuscular hemoglobin concentration. These data will assist in determining the etiology of anemia in a given population group. It is also suggested that blood smears should be made routinely in surveys. These can be saved and examined, when indicated, for size of cells or the presence of malaria parasites.

Another test for detecting iron deficiency is estimation of the level of serum iron. Both macro-[149] and micromethods[194] are available for this determination. The normal range for plasma iron is 0.05 to 0.180 mg. per 100 cc.[194] Low serum iron is not pathognomonic of iron deficiency, however, since Wintrobe,[214] Cartwright, *et al.*[33] and others have observed a diminished concentration in infections, both acute and chronic.

The normal range of values for hemoglobin has not been definitely established and is variously stated according to the method used and the interpretation of the investigator. Hemoglobin should always be expressed in grams, not in per cent of normal, and standards should be based on distribution curves which are characteristic of each age and sex group. In this country a commonly accepted standard of hemoglobin concentration in adults has been 14 ± 2 Gm. per 100 cc. of blood for females, 16 ± 2 Gm. for males.[214] Recently, several reports of hemoglobin concentration in college women have been published.[165, 167] Wintrobe[214] has suggested certain normal values for various age groups. Macy[127] found a range of 11 to 13 Gm. in a group of children judged to be in excellent health. Milam and Muench[146] have reported distribution curves for hemoglobin as found in a survey in North Carolina. These studies, and those carried out in Britain which will be mentioned subsequently, should assist in standardizing criteria of normalcy and in recognizing variations in hemoglobin which may be compatible with good health.

A high incidence of anemia has been found in surveys in the United States, particularly in children and pregnant women of the lower income groups.[44, 88] A survey of hemoglobin levels in 16,000 persons in Great Britain in 1943[161] was recently reported by the Medical Research Council, Committee on Hemoglobin Surveys. The Haldane-Gowers method, a visual colorimetric procedure, was adopted because of its wide use and simplicity. Dietary restrictions during the war did not cause deterioration of hemoglobin levels when comparison was made with previous data. Lower levels were found in women aged 40 to 49 than in other age groups and were considered to reflect blood loss and perhaps mild iron deficiency. In many instances hemoglobin concentration rose following iron therapy. The incidence of anemia in women was found to increase with the number of pregnancies. A similar relationship between pregnancy and anemia was reported in a survey in Newfoundland.[139]

Several English workers[45, 59] reported a decrease in anemia in Britain during the war years and ascribed this to an increase in iron intake with the use of National whole wheat flour. Hemoglobin levels have been reported to be higher in the United States than in England, on lower intakes of iron.[145] This seems to have been due to differences in methods used for determination of hemoglobin.[105] When the Haldane standard was recalibrated, the levels of hemoglobin in Britain were found to be closer to those in the United States.

In the famine areas of Europe during the Second World War, anemia was a frequent finding and in a large percentage of cases it was macrocytic with a high color index.[159, 160] Burger and coworkers[29] studied this type of anemia in Holland and found that liver, iron, and vitamins were without effect but that institution of a good diet brought about improvement. Cartwright and Wintrobe[34] found a high incidence of mild or moderate anemia, of macrocytic or normocytic type, in American military personnel who had been prisoners of the Japanese. Serum iron was slightly reduced in 55 per cent of the cases studied. The etiology of nutritional anemia not attributable to iron deficiency remains obscure, but it seems likely that deficiency of folic acid plays an important role and that lack of protein, "extrinsic factor," or some poorly defined substance in the vitamin B complex may be significant.

Shank,[194] using a micromethod for determination of serum iron, has reported that when the level falls below 60 micrograms per 100 cc., the administration of iron leads to a definite rise in hemoglobin; when the concentration of serum iron is greater than 60 micrograms per 100 cc., therapy with iron is without effect on the hemoglobin level. Waldenstrom[210] found iron deficiency a common problem in rural populations in Sweden. In one area, 22 per cent of the women examined had values for serum iron of less than 45 micrograms per 100 cc. Determination of serum iron should prove to be a most useful procedure in the assessment of nutritional status.

Darby and coworkers[43] have used radioactive iron in a mass study of school children in Tennessee and showed the feasibility of this procedure in surveys. In adults, the absorption of radioactive iron was greater in persons with iron deficiency than in normal subjects. In children, the up-take of iron was correlated with the estimated yearly increase of body iron during growth. There was no correlation with estimated intake, hemoglobin level, economic status, or general nutritive state.

In general, it may be stated that determination of the concentration of hemoglobin in the blood is a valuable procedure in appraising nutritional status if the method used is carefully applied, if its limitations are sufficiently appreciated, and if findings are interpreted with full realization of the variability consistent with normal health.

VITAMINS

The procedures most commonly used for evaluation of nutritional status in regard to vitamins include measurement of the level in the blood during fasting or after giving a test dose of the vitamin, and determination of the urinary excretion of the water-soluble vitamins. Excretion tests have included estimation of the output in one hour during fasting and "load" tests in which excretion is measured for a period of several hours after the oral or parenteral administration of a test dose. It is obviously impractical to determine excretion for twenty-four hour periods in surveys. The analysis of tissues obtained by biopsy has not been widely applied although this procedure offers possibilities which merit further investigation.

Johnson and coworkers[92] concluded from a study of normal persons on relatively constant diets that fasting specimens were preferable to loading tests and that random specimens of urine should not be used. When vitamin supplements were administered to one group of subjects, it was noted that the rate of excretion before breakfast was a more reliable index of intake in the previous few weeks than were vitamin load tests. These workers also reported that blood specimens might be collected at any time during the day without seriously influencing findings. The conclusions of Johnson *et al.* are not necessarily valid for population groups on varied and inconstant diets.

The value of vitamin load tests in determining nutritional status has been the subject of much controversy. Opinions vary in regard to mode of administration, proper dosage, time of collecting specimens, and interpretation of results. Johnson, Contreras, *et al.*[90] accomplished mathematical formulation of tolerance tests, both intravenous and oral, and suggested that collection of urine for one hour following an intravenous dose, and during the second hour after an oral dose (the periods of maximal excretion) might yield results comparable with those obtained from collections of four to ten hours respectively. However, great individual variation might be an invalidating factor. These suggestions have not as yet been subjected to critical tests.

Berryman and coworkers[10] reported a relationship between the immediately preceding dietary intake of a given vitamin and the average urinary excretion of this nutrient during fasting, but cautioned against using the fasting urinary level alone to diagnose nutritional status. At extremes of intake there was a high correlation between the dietary level and the urinary excretion during fasting. There was no significant correlation between fasting urinary levels and the response to load tests. These authors emphasized that there was no assurance that all subjects in a group would have the same range of excretion on the same diet. Individual differences in absorption and variations in renal threshold affect results, and there is some evidence that the volume of urine excreted may be significant. In the collection of one-hour specimens of urine, complete evacuation of the bladder is important. Lack of attention to this detail may invalidate findings. Accuracy will be greatly increased if specimens are collected over periods of two or three hours.

The repetition of load tests in normal persons at intervals of two to three weeks had no significant effect on the results of subsequent tests (fasting or load) according to Johnson and coworkers.[92] These findings would probably not apply to studies of persons with deficiency disease. Any combination of thiamine, riboflavin, or ascorbic acid could be given without influencing the excretion of the other vitamins, and niacinamide had no effect on the output of these vitamins. Johnson *et al.*[93] concluded that oral load tests were preferable to intravenous, in spite of possible differences in absorptive rate, because vitamin deficiencies due to poor absorption cannot be detected by injection, and it is difficult to maintain sterility in field studies. For the diagnosis of chemical deficiency, Johnson suggests that both a low excretion during fasting and a poor return after a test dose should be required, in view of the marked variation between individuals under similar dietary and environmental conditions. In interpreting findings, it should be remembered that in starvation tissues are being broken down and unexpectedly large amounts of certain nutrients may be excreted in the urine.[172]

Sinclair[195] stated that, in his opinion, no analysis of urine in rapidly conducted surveys could provide useful information regarding the state of nutrition. This view seems unduly pessimistic. The findings of many workers suggest that the urinary excretion of water-soluble vitamins reflects bodily stores and hence is of some assistance in evaluating the nutritional status of population groups even though absolute figures to divide normal from deficiency states are lacking.

VITAMIN A

Chemical tests for the evaluation of vitamin A nutrition in surveys have been limited to determination of the concentration of vitamin A and carotene in the blood. Tests of vitamin A absorption have been used in studying the nutritional status of individuals and in investigating problems related to vitamin A metabolism but have not been applied in mass examinations. The same is true of estimation of the vitamin A content of liver tissue obtained by biopsy.

Procedures for the determination of vitamin A in blood have included a colorimetric method based on the Carr-Price reaction in which an unstable blue color is formed by the interaction of vitamin A and antimony trichloride, and an ultraviolet absorption method in which the light absorption of a solution of the vitamin is measured at 328 μ with a spectrophotometer. Carotene has been determined by the solvent partition method and by the chromatographic technic. Chemical methods involving the Carr-Price reaction have been described by Kimble,[103] Dann and Evelyn,[42] Clausen and McCoord,[36] May *et al.*,[132] and others. When these methods are used, the carotene content of the material must be simultaneously determined since it also forms a blue color with antimony trichloride. The intensity of the blue color is read at 660 μ for vitamin A, 446 μ for carotene, and the proper correction applied. Both the ultraviolet absorption procedure and the Carr-Price reaction have numerous drawbacks but are the only ones widely tested. Errors due to interfering substances can be serious. Bessey *et al.*[18] have described a microtechnic for the determination of vitamin A and carotene in blood which should be particularly useful in surveys. The method depends on saponification and extraction of vitamin A and carotene from 60 cu. mm. of serum, and measurement of the light absorption at 328 and 460 μ, followed by destruction of vitamin A and remeasurement at 328 μ. A detailed description of methods for determining vitamin A and carotene and a brief discussion of their application can be found in several recent publications.[19, 140]

The normal range of values for vitamin A and carotene in the blood has not been completely determined. Among various groups of healthy individuals carotene has ranged from 50 to 400 micrograms per 100 cc. of blood.[1, 103, 185, 216, 219] It has been suggested that the lower limit of normal be placed between 50 and 100 micrograms per 100 cc. for carotene, 40 and 75 I.U. for vitamin A.[18, 132, 185, 219] In more recent studies the concentration of vitamin A has been expressed in micrograms, and Bessey[12] has suggested that the normal range is from 30 to 70 micrograms per 100 cc. of blood. Jolliffe[96] has considered 20 to 30 micrograms as the lower limit of normal. In studies of hospitalized patients[69] and in a number of nutrition surveys,[216] mean levels of both vitamin A and carotene in the blood have been lower than in normal healthy adults. In surveys in Tennessee and North Carolina[4] no correlation was found between vitamin A intake, plasma level, and clinical signs which were considered evidence of vitamin A deficiency. Krause and Pierce[112] found no difference in the concentration of vitamin A in the blood in children with and without folliculosis. In a survey in Newfoundland[2] where the intake of vitamin A was found to be low, the levels in the plasma were likewise low and the incidence of clinical signs attributed to vitamin A deficiency was high.

In healthy adults Hsu[84] found the average concentration of vitamin A in the blood to be 56 I.U. per 100 cc. (range 30 to 104 I.U.); of carotene 140 micrograms per 100 cc. (range 85 to 226 micrograms). In hospital patients without signs of vitamin A deficiency, the average value for vitamin A was 33 I.U. (range 0–132) and for carotene 65 μg. (range 0–197). In patients with clinical signs of vitamin A deficiency, averages were 6 I.U. for vitamin A (range 0–27) and 24 micrograms for carotene (range 0–141).

It seems apparent that there is a relationship between the amount of vitamin A and carotene in the blood and clinical evidence of vitamin A deficiency, but wide individual variations occur and a given level should be interpreted with caution. Moreover, it is well known that the concentration of vitamin A in the blood is decreased in many types of disease.[178, 200] In normal experimental animals there is good correlation between vitamin A in the blood and liver reserves.[178] Aron *et al.*[5] have stated that levels of vitamin A and carotene in the blood are an expression of liver function. When the intake of vitamin A is reduced, blood levels decrease very slowly in adults, but in children reduction may be noted in two to four months. Yudkin[222] has pointed out that the quantity in the blood may be influenced by recent diet and may rise when signs of deficiency are still present. Aside from this, a normal level of vitamin A in the blood is not apt to occur in clinically manifest deficiency. It has been shown that supplements of vitamin A and carotene during pregnancy[118] will prevent the decrease which commonly occurs in the concentration of vitamin A in the blood.

In summary, a low level of vitamin A in the blood may mean vitamin A deficiency, decreased reserve stores, or the presence of some disease which affects vitamin A metabolism. Determination of vitamin A and carotene in the blood would appear to be more meaningful in group studies than in individual nutritional appraisal. Low levels suggest deficiency but should be correlated with other findings for definite diagnosis.

VITAMIN B COMPLEX

Chemical tests for three members of the vitamin B complex, thiamine, riboflavin, and niacin, have been extensively studied and applied to surveys. Excretion of other B vitamins such as pyridoxine, pantothenic acid, biotin, etc., have been included in certain investigations, but their importance in nutritional appraisal has not been demonstrated.

THIAMINE

The tests most frequently used in surveys in evaluating thiamine nutrition have been determination of the excretion in the urine for a one-hour period during fasting or for several hours following the administration of oral or parenteral test doses of this vitamin. Other tests have included measurement of thiamine in the blood or in tissues obtained by biopsy,[57] determination of cocarboxylase in the blood,[64] and estimation of blood pyruvic acid[27, 58] and of the blood lactate-pyruvate ratio[62, 202] during fasting, after glucose, and following exercise. Some of these procedures are more useful in appraising individual status than in evaluating the nutrition of population groups.

Methods for the determination of thiamine in urine have included: (1) the yeast fermentation procedure[193] which lacks specificity and gives higher values than other methods but has the advantage of measuring phosphorylated thiamine without hydrolysis (a technic for inactivating thiamine can be included); (2) a colorimetric method[134] using para-aminoacetophenone, the technic of which is laborious and which is not applicable to materials of very low thiamine content; and (3) the thiochrome method[74] which has been variously modified, has high sensitivity, and is applicable to material of low thiamine content but requires considerable time for completion. Perlzweig[169] has recently developed a modified thiochrome technic for rapid use in surveys. A disadvantage of the thiochrome technic is that urine contains non-thiamine fluorescent substances which may cause gross errors, particularly in urines of low thiamine content. In order to overcome this difficulty, Mason and Williams[131] suggested destruction of thiamine with sulfite to obtain a blank value, while Najjar and Ketron[157] measured fluorescence of a reagent blank and an alkali-treated aliquot and applied a correction factor. Mickelsen, Condiff, and Keys[142] eliminated interfering substances by control of acidity in the final extraction stage.

The urinary excretion of thiamine has been widely studied and more is known about the output of this vitamin at various levels of intake, and about the relationship between clinical and laboratory findings, than for any other member of the vitamin B complex. The urinary excretion of thiamine appears in a general way to be linearly related to thiamine intake. Mickelsen, Caster, and Keys[141] have shown, with statistical methods, that the excretion of thiamine is highly characteristic of the individual, as well as of the intake, and that variability in data becomes more marked as thiamine intake increases. They have suggested determination of both thiamine and pyramine, a pyrimidine-like component of the thiamine molecule which is excreted in the urine, in evaluation of thiamine nutrition when the intake of thiamine is unknown. At low levels of thiamine intake, the excretion of pyramine is still determinable, whereas the excretion of thiamine itself becomes zero. There is considerable disagreement in the literature in regard to the quantitative output of thiamine on low intakes and concerning the levels of excretion which may be considered indicative of normalcy and deficiency. This is particularly true in the interpretation of findings after test doses have been administered.

The excretion of thiamine has been shown to fall rapidly when the intake of this vitamin is lowered.[47, 66, 78, 130, 133, 163, 212, 213] However. Holt and Najjar[80] reported that the excretion may be at minimal levels for several months before signs of clinical deficiency appear. Mickelsen *et al.*[141] stated that with an intake of about 0.7 mg. per day the thiamine excretion approached zero. Similar findings were obtained by Berryman.[10] Hulse *et al.*[87] suggested that the urinary excretion of thiamine reflected changes in the concentration of freely diffusible and extracellular thiamine.

The amount of thiamine excreted in a one-hour fasting specimen has been considered by many investigators[80, 92, 163, 166] to be useful in evaluating nutritional status, correlating well with the average daily intake. The exact quantity which is indicative of deficiency has been stated to be zero by Holt,[80] 0.6 microgram by Johnson,[93] and 4 micrograms by Papageorge and Lewis.[166] Variation in interpretation is dependent on the definition of deficiency by the individual investigator. Correlation between the one-hour fasting excretion and the twenty-four-hour excretion has been reported by Melnick and Field,[137] Papageorge and Lewis,[166] and others. Holt[77] considers that the fasting one-hour excretion is less liable to fluctuation due to changes of intake than the twenty-four-hour excretion. The degree of deficiency cannot be detected by either the one-hour fasting or the twenty-four-hour excretion.

There is even more disagreement in regard to the interpretation of load tests. It is agreed that in persons on controlled intakes, the excretion following the administration of a test dose decreases as the intake of thiamine is reduced. Delineation of the level which may be diagnostic of deficiency has not been accomplished. Najjar and Holt[78] have found that thiamine excretion, after administration of 1 mg. of the vitamin intravenously, drops to less than 50 micrograms in four hours when symptoms of thiamine deficiency appear. Williams and Mason[130, 212, 213] stated that an excretion of less than 100 micrograms with this test indicated moderate deficiency, less than 50 micrograms severe deficiency. Excretions of this low order occur only when the dietary intake is approximately 0.2 mg./1000 calories or less.

Johnson[93] used an oral load test in which 5 mg. of thiamine was administered and concluded that an output of less than 20 micrograms in four hours was subnormal. With this same test, Goldsmith and Sarett[63] found that 7 persons on normal diets excreted over 150 micrograms in four hours; 5 subjects on diets containing 0.2 to 0.3 mg. of vitamin B_1 per 1000 calories excreted less than 50 micrograms. Melnick and Field[137] reported lower excretions in deficient than in normal subjects with load tests in which thiamine was given intramuscularly. Ruffin *et al.*[185] reported a significant difference in the excretion of thiamine in a four-hour period by normal persons and patients with clinical findings of mild deficiency of the B vitamins, when 1 mg. was given intramuscularly. Oldham *et al.*[163] concluded that load test excretions gave a better idea of tissue stores than did the output in one hour during fasting or in a twenty-four-hour period.

Of other tests available for assessing thiamine nutrition, estimation of the thiamine content of whole blood and of the erythrocytes and leukocytes merits further study. Foltz *et al.*[57] reported that the thiamine content of whole blood tends to correspond to the character of the diet but does not correlate well with urinary excretion. Greenberg and Rinehart[65] found the thiamine content of whole blood relatively static and not readily affected by changes in intake. Oldham *et al.*[163] reported a decrease in thiamine levels in the blood when the thiamine intake was 0.14 mg. per 1000 calories. Hennessy[73] emphasized that virtually all of the thiamine of blood is found in the cellular elements, so that a mere statement of findings without including an hematocrit determination is almost meaningless. It is preferable to know the thiamine content of the total cells, the hematocrit, and the white count. Erythrocytes contain about 8.6 micrograms, and leukocytes 70.6 micrograms per 100 cc. Studies of the thiamine content of the white cell-platelet layer might be profitable.

The estimation of cocarboxylase in whole blood was considered by Goodhart and Sinclair[64] to be a reliable method of evaluating saturation of the tissues with thiamine while determination of thiamine in plasma was not satisfactory. Hennessy[73] has stated that there is almost no free thiamine in plasma. Hulse[87] reported a decrease in the yeast-stimulating activity of plasma in subjects on a diet low in thiamine. Further investigation is certainly needed before any of these tests can be applied in surveys.

Pyruvic acid determinations during fasting, after glucose, or after exercise are useful in evaluating thiamine nutrition, particularly in individuals. These methods require considerable care, are time-consuming, and are not readily applicable to surveys. Furthermore, many pathologic conditions other than thiamine deficiency are associated with a rise in pyruvic acid in the blood. Stotz and Bessey[202] suggested that the determination of both pyruvic and lactic acids, with computation of the lactate-pyruvate ratio, was of assistance in evaluating thiamine nutrition. Goldsmith[62] reported similar findings. Determination of blood pyruvate or of the lactate-pyruvate ratio after a standard exercise test may be informative of nutritional status and is worthy of further investigation.[62, 101] Melnick[137] stated that urinary thiamine values were more sensitive indicators of changes in thiamine intake and of thiamine stores than were tests related to carbohydrate metabolism.

The thiamine content of muscle has been shown to decrease in thiamine deficiency.[87] Muscle biopsies are not difficult to obtain and studies of the concentration of thiamine and other vitamins in such specimens should be undertaken.

RIBOFLAVIN

Methods for the determination of riboflavin which are applicable to surveys include estimation of the quantity in the blood (serum and erythrocytes) and measurement of the urinary excretion for one hour during fasting and for several hours after the oral or parenteral administration of a test dose of riboflavin. Two types of procedures for the determination of riboflavin have been commonly employed, microbiologic and fluorometric. In the microbiologic method,[198] *Lactobacillus casei* is the test organism and bacterial response is measured by titration of acid formed or turbidometrically. The fluorometric procedures have included those of Hodson and Norris[75] and of Conner and Straub[38] with numerous modifications. Ferrebee[55] introduced a "direct" method in which the absorption procedure was omitted, and Najjar[151] proposed a fluorometric method applicable to biologic materials. Bessey and Lowry[15] developed a micromethod in which riboflavin is determined in 15 cu. mm. of red cells by the rate of acid production by *Lactobacillus casei*. Fluorometric methods check well with the microbiologic procedure if interfering fluorescent substances can be removed. This is at times difficult or impossible with biologic materials such as urine. The direct method of Ferrebee[55] or Johnson's field method[89, 94] are more rapid for mass studies but less accurate. The microbiologic test is more specific and has a high degree of accuracy but requires considerable time and equipment.

In general, the amount of riboflavin excreted in the urine parallels the dietary intake until high levels are reached, at which time quantitative excretion is increased but the percentage of the intake excreted is little affected.[26] Excretion may be dependent in part on the protein content of the diet.[190, 191] Furthermore, Perlzweig[168] has shown that after four days of fasting, riboflavin excretion may be very high. Sure and Ford[204] reported a marked increase in the output of riboflavin in experimental animals when the diet was restricted in thiamine.

The excretion of riboflavin in one hour during fasting has been used by Holt and Najjar,[80] Johnson *et al.*,[92] Kark, Bean, *et al.*,[99] and others, as an index of nutritional status. Kark, Bean *et al.*[99] showed a good correlation between the intake of riboflavin and the fasting one-hour excretion of this vitamin. Brewer[26] found good correlation between the average excretion in twenty-four hours and in one hour during fasting. Similar findings were reported by Davis *et al.*[46] up to a certain level of intake. Hagedorn[67] reported fair agreement of the output in one hour with that in twenty-four hours. Johnson[93] has suggested that a fasting excretion of less than 20 micrograms per hour (with a rapid fluorometric method) is indicative of chemical deficiency. Cogswell *et al.*,[37] in a study of subjects on diets containing 0.3 mg. of riboflavin daily, found an excretion averaging 16 micrograms in one hour. Holt[79] considered a level approaching zero evidence of deficiency. In infants on a diet free of riboflavin, he found a minimal twenty-four-hour urinary excretion of 40 to 50 micrograms, which would be about 2 micrograms per hour. Goldsmith and Sarett,[63] using the microbiologic method, found an excretion of 2 to 5 micrograms in one hour during fasting in 3 patients maintained for five to six weeks on a diet containing 0.5 mg. of riboflavin daily. The exact values reported by several groups of workers cannot be compared because of differences in the methods used.

Feder, Lewis, and Alden[54] reported that measurement of riboflavin in terms of concentration per cubic centimeter of urine gave a better index than did concentration per unit of time. Hathaway,[71] however, found no relationship between riboflavin excretion and urinary volume. Kark,[99] found a lower fasting excretion among Indians than among occidental troops. In the former, folliculosis, corneal invasion, and cheilosis were frequent findings. Hou and Dju[82] found twenty-four-hour riboflavin excretion lower in patients with glossitis, cheilosis, and eye signs of riboflavin deficiency than in normal persons. The amount of riboflavin excreted was usually proportional to the volume of urine and paralleled thiamine excretion.

The usefulness of load tests in evaluating riboflavin nutrition is the subject of much controversy. The size of the test dose has varied markedly and the usual differences of opinion have been expressed concerning the merits of oral or parenteral administration. Johnson[93] used a 5 mg. oral dose and considered an output of less than 200 micrograms in four hours evidence of unsaturation. Goldsmith and Sarett[63] in a study of 5 individuals maintained for five to six weeks on a diet containing 0.5 mg. riboflavin, found an excretion of 1.1 to 1.6 mg. in four hours after giving 5 mg. orally, while a small group of well-nourished persons excreted 1.5 to 3.9 mg. Davis *et al.*[46] noted a progressive increase in riboflavin excretion after an oral test dose of .02 mg. per Kg. body weight as dietary levels were raised from .29 to .66 mg. of riboflavin per 1000 calories. No further increase occurred with higher intakes.

Brewer[26] found good correlation between the average excretion in twenty-four hours and the excretion for four hours after an oral dose of 3 mg. Correlation between the one-hour fasting excretion and the test dose was not significant. Feder *et al.*[54] found a coefficient of correlation of .61 between the fasting excretion and the percentage of the test dose (.016 mg. per Kg. intramuscularly) recovered in the urine. They concluded that saturation levels seldom gave more information than the fasting morning specimen. Hagedorn *et al.*[67] found that the retention of riboflavin supplements varied widely without apparent reason, and criticized the use of load tests as evidence of riboflavin deficiency.

Riboflavin in blood has been measured by the microbiologic method, using either macro-[25, 203] or micro-[15] procedures. Axelrod *et al.*[8] found no difference in the riboflavin content of the blood of normal persons and of patients with riboflavin deficiency. Holt[79] has recently studied infants on a riboflavin-free diet and found that riboflavin disappeared from the serum and that there was a marked reduction in the content of the erythrocytes and leukocytes. When the dietary intake of riboflavin was increased to 0.40 to 0.45 mg. per day riboflavin was again present in the serum and the level in the erythrocytes and leukocytes returned to normal. Riboflavin was determined with the method of Burch, Bessey, and Lowry,[28] which requires special apparatus not readily available. Determination of riboflavin in blood, particularly in the cellular components, may prove useful in nutritional surveys and deserves further investigation.

NIACIN

Chemical tests for the appraisal of niacin nutrition have been numerous but far from satisfactory. Niacin is excreted in the urine in various forms, as N^1-methylnicotinamide, small amounts of nicotinamide and nicotinic acid, as nicotinuric acid, and in the form of a pyridone compound. Niacin and its amide may be determined by a microbiologic procedure using *L. arabinosus* as the test organism[113, 199] or by chemical methods involving the König reaction, with cyanogen bromide and an aromatic amine, to form a colored compound.[19]

Various procedures including hydrolysis with strong acid or alkali and removal of interfering substances, followed by application of the cyanogen bromide reaction[135, 136, 170] have been used for measurement of niacin derivatives. The most important of these was thought at one time to be trigonelline but was later shown to be N^1-methylnicotinamide. Procedures for the fluorometric determination of N^1-methylnicotinamide (F2) have been devised by Najjar and Wood,[158] Huff and Perlzweig,[85] and others. A simplified and sensitive method involving condensation of N^1-methylnicotinamide with acetone, in alkaline solution, has recently been proposed by Huff and Perlzweig.[86]

Recently Knox and Grossman[109] have isolated a pyridone from urine, N^1-methyl-6-pyridone-3-carboxylamide, which seems to be the major excretory product of niacin.[108] The method for determination of this pyridone is at present extremely difficult and simplification is essential for application to studies of human niacin nutrition. Rosen, Perlzweig, and Handler[184] have recently developed a procedure which may fill this need.

In the analysis of whole blood for niacin, results should be expressed in terms of hematocrit values, or red cells, since practically all the niacin is found in the erythrocytes, the amount in the plasma being negligible. The nicotinic acid of the cells is present almost entirely as pyridine nucleotides.[107] Microbiologic assays employing *Hemophilus influenzae* and *parainfluenzae* are available for determining these metabolites and are simpler than chemical procedures. The fluorometric method employing condensation with acetone has recently been applied to the determination of pyridine nucleotides in cells and tissues.[86] Carter and O'Brien[32] studied normal persons and patients with various diseases and concluded that the concentration of niacin in blood did not provide a useful nutritional guide. Axelrod *et al.*[7] and Kohn and Bernheim[110] reported that the determination of coenzyme I in the blood offered little diagnostic information in borderline cases of deficiency disease. These workers found an increase in coenzymes after niacin was administered. Youmans[217] stated that the level of coenzymes in blood failed to show close correlation with niacin deficiency. Vilter and associates[208] found that the blood level of codehydrogenase was lower in 3 pellagrins than in 4 normal persons.

Blood methods have not been used extensively in the investigation of niacin metabolism and there is a paucity of data concerning the levels of pyridine nucleotides in whole blood, or in the cellular elements, at various levels of nutrition. Further investigation along this line may be worth while despite the negative findings indicated above.

Numerous studies of the excretion of niacin derivatives in the urine have been carried out. There is little change in the urinary excretion of freely hydrolyzable derivatives of niacin with variations in diet, and only a slight decrease occurs in pellagra. Early reports, with the use of cyanogen bromide methods, showed that the urinary excretion of "trigonelline" was decreased in persons with niacin deficiency. A diminished output was found both in twenty-four-hour specimens and in urine collected following the administration of a test dose of niacinamide.[56, 61, 173]

In recent investigations the excretion of N^1-methylnicotinamide has been measured in the fasting one-hour urine and after the administration of a test dose of niacinamide. Many difficulties are involved in interpreting findings in these tests. The excretion of N^1-methylnicotinamide accounts for only about 20 to 30 per cent of niacinamide given as a test dose.[39, 189] Wide variations have been observed between individuals in the percentage of niacinamide excreted as methyl derivatives. The rate of methylation, or the available methyl supply of the body, may be important in this regard. However, determination of N^1-methylnicotinamide appears to be the only procedure, applicable to urine, which is practical at the present time for use in surveys.

It is generally agreed that findings obtained should be interpreted with caution in evaluating niacin nutrition. Mickelsen and Erickson[143] found no difference in the excretion of subjects receiving 0.1 to 22 mg. of niacin per day over a period of one month. They concluded that determination of N^1-methylnicotinamide in the twenty-four hour urine was of little value. Ruffin *et al.*[185] and Sargent *et al.*[192] reported that the urinary excretion of N^1-methylnicotinamide correlated reasonably well with dietary and clinical evidence concerning bodily niacin stores. Najjar *et al.*[152, 153, 156] reported the disappearance of F2 in pellagra and its reappearance after vigorous therapy. They proposed the routine measurement of F2 in surveys and suggested that if this substance was absent from the urine in the post-absorptive state, the niacin stores were low. Johnson[93] considered that an excretion of .03 mg. of N^1-methylnicotinamide, or less, in one hour during fasting indicated unsaturation. However, it has been shown that normal persons occasionally excrete no N^1-methylnicotinamide in the fasting specimen.[192] Perlzweig *et al.*[168] found little change in the excretion of N^1-methylnicotinamide during a four-day fast and Sargent[192] reported a high output in one man who fasted sixteen days. Cayer and Cody[35] found an increased excretion of niacin derivatives in sprue associated with marked muscle wasting.

Following the administration of a test dose of niacinamide, there is a prompt rise in N^1-methylnicotinamide excretion in normal subjects, reaching a maximum in two to four hours.[39, 77, 80, 154, 155] Occasionally a normal individual fails to show this increase.[192] A high excretion of N^1-methylnicotinamide may be more significant than a low excretion in the absence of prolonged fasting or wasting of muscles. Johnson[93] has suggested that an excretion of less than 0.5 mg. in four hours after administering 50 mg. of niacinamide orally indicates chemical deficiency. Cogswell *et al.*[37] showed that a decrease in N^1-methylnicotinamide excretion after an intravenous dose of niacinamide occurred in 7 patients on a diet deficient in the B vitamins.

There are numerous reasons for the discrepancy of findings obtained by these and other investigators. Many different methods of analysis have been used and wide variations between individuals and in the same individual on different days have been demonstrated. As previously noted, there may be marked individual differences in the percentage of various metabolites of niacin which are excreted. Such differences may be due, in part, to the methylating ability of the organism. Furthermore, as Knox[108] has shown, N^1-methylnicotinamide is not the major metabolite of niacin excreted in the urine of man.

A still more important factor leading to confusion in interpretation of data may be the relationship between tryptophane and niacin metabolism. Sarett and Goldsmith[187] and Perlzweig and coworkers[171] showed a marked increase in the excretion of N^1-methylnicotinamide following the administration of tryptophane to persons on both normal and restricted diets. The increase appeared to be proportional to the amount of tryptophane given.[188] Analysis of diets for tryptophane, as well as for niacin content, is essential if any correlation between dietary intake and urinary excretion is attempted. The whole field of niacin metabolism needs reevalution. Studies at various levels of niacin and tryptophane intake, including investigation of patients with clinical pellagra, must be carried out. The urinary excretion of the pyridone compound of niacin[109] must be measured under various experimental conditions. It should not be too long before better tests are available and more accurate knowledge of the value of present tests can be ascertained.

One may conclude that, at present, the determination of N^1-methylnicotinamide in the urine during fasting and after the administration of a test dose of niacinamide are worth-while procedures in the assessment of nutritional status if conservative interpretation is applied to the findings.

Ascorbic Acid

Ascorbic acid has been one of the most extensively studied of the essential nutrients and numerous tests have been proposed for the appraisal of ascorbic acid nutrition. In comparing the merits of various methods, evaluation would be much easier if some standardization of procedures had been attempted. Lack of agreement is particularly frequent in regard to load tests which are almost as numerous as the investigators working in this field.

In the measurement of vitamin C in biologic materials, the oxidation-reduction properties of ascorbic acid are widely used as the fundamental reaction. The reducing capacity of acid extracts of the test material are measured by treatment with an oxidizing reagent of which 2,6 dichlorophenolindophenol has been found the most satisfactory. Visual titration technics[14, 53, 70, 207] and photometric methods[11, 30, 148, 182] based on this reagent have been applied in analyses of blood and urine. Visual titration may be inaccurate in extracts which contain water- or acid-soluble pigments, or reducing agents other than ascorbic acid which react rapidly with the dye, producing interference with the end point. Photometric methods partially overcome these difficulties. Many procedures for the removal of pigments and of interfering reducing substances have been suggested.[19] Dehydroascorbic acid may be determined by the reaction with 2,4 dinitrophenylhydrazine to form an osazone which is converted to a red pigment upon treatment with sulphuric acid. This is the basis of the Roe and Oesterling[183] method for determining total ascorbic acid of whole blood and urine, and of the micromethod of Bessey, Lowry, and Brock[17] for estimation of ascorbic acid in blood. These methods are rapid and possess a high degree of specificity.

Tests for assessment of nutritional status include determination of the level of ascorbic acid in the plasma, whole blood, and white cell and platelet layer, and estimation of the urinary excretion during fasting and in a twenty-four-hour period. In addition, a number of load tests have been proposed in which changes either in blood levels or in the urinary excretion of ascorbic acid are determined for varying periods of time after administering an oral or parenteral dose of ascorbic acid.

The level of ascorbic acid in the plasma during fasting corresponds in general with the dietary intake of this vitamin.[52, 68, 99, 164, 206] Determination of this level has been a method commonly used in surveys because of the ease with which specimens can be obtained and the relative simplicity of the laboratory procedure. The significance of findings has been extremely controversial. Temporary fluctuations in plasma ascorbic acid are frequent[114] and there is a wide range of values at any given level of intake. Dodds and MacLeod[49] have recently reported mean values, together with ranges and standards of deviation, for 41 women receiving 32, 57, 82, and 107 mg. of vitamin C daily. These and similar findings should be useful in interpreting survey data. If recent intake has been liberal, 75 to 100 mg. daily, values of 1.0 to 1.4 mg. per 100 cc. will be obtained; if only 15 to 25 mg. has been included in the diet, values of 0.1 to 0.3 mg. will be found.[162]

Controversy has been chiefly concerned with the meaning of low levels of plasma ascorbic acid and determination of the point at which a deficiency state may be said to exist. Levels ranging from 0.3 to 0.7 mg. per 100 cc. of blood have been suggested as the lower limit of normal by various workers. If concentrations below these levels indicate an unsatisfactory state of nutrition, large segments of the population fall in this classification.[88] In the opinion of several investigators, levels as low as 0.1 to 0.3 mg. per cent are not indicative of deficiency but merely reflect a low recent dietary intake or suggest that the body is not saturated with vitamin C. It has been emphasized that unsaturation is compatible with normal health. Ruffin *et al.*,[185] Johnson *et al.*,[91] and others have reported plasma levels of zero in persons without clinical signs of scurvy. Johnson found that when healthy adults were placed on a diet containing no vitamin C, the serum ascorbic acid fell to zero in about eight weeks. In Crandon, Lund, and Dill's experiment,[40] plasma levels were zero for thirteen weeks before clinical scurvy became evident, while leukocyte levels reached zero just prior to this. Lowry *et al.*[122] and Linghorne[119] noted a fall in the ascorbic acid of the serum to 0.2 mg. per 100 cc. on a daily intake of either 8 or 23 mg. of ascorbic acid. A definite relationship was shown to exist between the concentration in the serum and in the white cells. Serum levels of 0.4 mg. per 100 cc. or above were associated with concentrations in the leukocytes of more than 20 mg. per 100 cc. while serum levels under 0.3 mg. per 100 cc. were associated with concentrations in the leukocytes of less than 20 mg. per 100 cc. With a white cell value of one-half of normal, serum ascorbic acid was not zero but measured 0.1 to 0.4 mg. per 100 cc. Realimentation studies indicated that the leukocytes appeared to be a valid index of total body concentration.

Bessey[15] found measurable differences in ascorbic acid in the serum of three groups of New York school children of different economic background. Farmer[52] found that in normal men, on a diet containing 0 to 10 mg. of vitamin C, the plasma ascorbic acid reached zero in seventy days. Serum levels below 0.3 mg. per 100 cc. have been considered indicative of chemical deficiency by Johnson.[93] Dogramaci[50] found plasma levels of 0.1 to 0.3 mg. per 100 cc. (average .087) in 24 cases of scurvy. Vilter *et al.*[209] reported levels of 0.0 in 19 adults with scurvy and McMillan and Inglis[124] a mean of 0.05 mg. per cent in 22 subjects with this deficiency disease. Johnstone[95] found that a marked change in intake will be reflected by a change in the concentration in the blood during fasting in one to two weeks. Milam and Wilkins[147] showed that low plasma levels could be raised in a six-week period by feeding an adequate diet.

Munks,[150] in a study of vitamin C nutrition in pregnancy, concluded that determination of ascorbic acid in the blood and urine was an unreliable index of nutritional status. Smith[197] stated that ascorbic acid in maternal blood was correlated with the dietary intake and with the level in the cord blood of the infant. In numerous disease states there is a decrease in the concentration of plasma ascorbic acid. This should be considered in evaluating results in studying certain weighted samples of the population.

In the majority of studies, little or no correlation has been demonstrated between the amount of ascorbic acid in the plasma or the degree of saturation of the tissues with vitamin C, and changes in the gums ascribed to deficiency of this nutrient.[3, 44, 116, 125, 145, 211] In a few studies, the incidence of gingivitis appeared to be related to ascorbic acid intake or to plasma levels.[115, 119, 209] In experimental deficiency, gum changes do not occur before other signs of scurvy.[40, 52]

Although low concentrations of plasma ascorbic acid are found in the absence of clinical scurvy, this does not mean that such findings are of no significance. If the mean plasma level in a population group is low, it appears likely that the intake has been poor for long periods of time and suggests that bodily stores have been depleted. Plasma levels of less than 0.3 mg. per 100 cc. may be considered suggestive of chemical deficiency.

The only tests of urinary excretion which can be used in surveys are those requiring brief periods for collection. The excretion in one hour during fasting or in several hours after a test dose of ascorbic acid may be determined. Close correlation has been reported by Johnson[92] between the average daily intake of ascorbic acid and the excretion in the urine before breakfast. The significance of this correlation has been questioned by Berryman.[10] Interpretation of findings in the fasting urine in group surveys should be conservative.

Load tests for the assessment of ascorbic acid nutrition have employed varied dosage (either according to body weight or an arbitrary amount) administered orally or intravenously, and collection periods for urine or blood have ranged from one to twenty-four hours. In the evaluation of these tests, a certain percentage of the test dose excreted has been considered indicative of saturation, another percentage of deficiency. These percentages have been chosen by comparing findings in normal persons with those in patients with deficiency disease or by testing individuals under carefully controlled experimental conditions on various levels of intake. The numerous procedures suggested cannot be enumerated here.[196, 217] A few recent studies will be mentioned which bear on the validity and interpretation of load tests.

Johnson, Darling, *et al.*[91] showed that the excretion of ascorbic acid for three and six hours after giving 1 Gm. of the vitamin orally, definitely reflected the intake of subjects whose bodily stores were known to be very low, average, or high by virtue of subsistence on diets lacking, normal, or high in vitamin C. The level of serum ascorbic acid was distinctly different in the deficient and supplemented groups. In another study, Johnson and coworkers[93] suggested that an excretion of less than 3 mg. in four hours after an oral test dose of 500 mg. of ascorbic acid was indicative of chemical deficiency.

Farmer[52] studied normal men on a diet containing 0 to 10 mg. of vitamin C daily and conducted a saturation test employing an oral dose of 15 mg. per Kg. of body weight, with measurement of ascorbic acid in the blood and urine every hour for five hours. This test was reported to be a reliable index of tissue depletion. Holland *et al.*,[76] using the saturation test of Wright and coworkers[215] (1 Gm. of ascorbic acid intravenously with determination of the one-and-a-half- and five-hour urinary excretions), found a satisfactory correlation between the five-hour excretion and the fasting level in the plasma in 85 per cent of 48 cases. Haines *et al.*[68] found that on daily intakes of 33 to 70 mg., the excretion in twenty-four hours after an oral test dose of 400 mg. corresponded with the intake. Youmans[217] pointed out that the findings with load tests paralleled findings in the plasma during fasting.

Kajdi *et al.*[98] concluded that a correlation existed between load tests and the clinical diagnosis of ascorbic acid deficiency or adequacy in infants. The test consisted of measurement of plasma ascorbic acid four hours after the intramuscular injection of 200 mg. of ascorbic acid.

Berryman[10] concluded that correlation between the urinary excretion during fasting and the excretion following load tests appeared to be good at extremes of intake but less significant at intermediate levels. Kark *et al.*[99] found correlations between the intake of ascorbic acid, the concentration in the serum, and the urinary excretion in a study of troops in tropical areas.

In various surveys, low concentrations of plasma ascorbic acid have been interpreted as indicative of a high incidence of deficiency of this vitamin. It would be better to state that the dietary intake had been low, that ascorbic acid reserves were reduced in a large sample of the population, and that chemical deficiency was presumably present in a certain percentage of this group. Investigation of the dietary history, measurement of ascorbic acid in the leukocytes, and the administration of load tests, can give additional information regarding the presence and severity of tissue depletion. Plasma levels mirror more closely the diet; white cell levels, the tissue stores.

VITAMIN D AND CALCIUM

In the appraisal of nutritional status in regard to calcium and vitamin D, only two procedures have been used in nutritional surveys: the determination of the level of calcium in the blood and the measurement of alkaline phosphatase in the serum. There are, at present, no chemical methods which permit estimation of vitamin D in biologic materials of low potency.[19] Studies of vitamin D in the blood are impractical and studies of excretion are lacking.

It has been recognized for a number of years that alkaline phosphatase increases in the serum in rickets and in a number of other diseases associated with abnormalities in the metabolism of bone. In 1933, Bodansky[21, 22] proposed a method for determining alkaline phosphatase which has been used extensively. In 1946, Bessey *et al.*[16] developed a microprocedure using 3 to 20 cu. mm. of serum in which the amount of enzyme was measured with p-nitrophenyl phosphate as the substrate. There was only slight divergency of results with the two methods. The normal level of alkaline serum phosphatase is stated to be 3 to 12 Bodansky units in children up to the age of 12, and 3 to 5 units in adults. Klasmer[106] found values of 5.6 to 15 units in 320 healthy children between the ages of 6 months and two and one-half years.

Alkaline serum phosphatase is elevated early in rickets and parallels the activity of the disease and the healing process. In mild rickets, the level may be 20 to 30 units, in severe rickets as high as 60 units.[23, 24] Determination of serum phosphatase is a reasonably reliable and accurate, although not specific, method of diagnosing early rickets and hypovitaminosis D. Other causes of an increase in phosphatase activity are uncommon at the age when rickets is prevalent and are easily detected.[217] In adults and children over 5 years of age, elevation of alkaline phosphatase in the serum is uncommon[220] and has been considered to be of doubtful significance. Recently Bessey[13] has found a slight increase in phosphatase in certain groups of children and has suggested that determination of this enzyme may be a useful tool, comparable to hemoglobin, in nutrition surveys. More data should be obtained in persons of all age and sex groups and under various conditions of metabolic activity. Many diseases are of etiologic importance in variations in the concentration of phosphatase in older persons, and the likelihood of a relationship to vitamin D deficiency is not great. In China, a decided increase in phosphatase activity has been noted in osteomalacia. In a recent survey in Newfoundland, it was concluded that vitamin D deficiency was infrequent because few clinical signs of rickets were observed and low serum phosphatase values were obtained.[2] The value of including phosphatase determinations in surveys, other than those involving infants and young children, remains to be determined.

Determination of the calcium and phosphorous content of blood has been used in the diagnosis of rickets and osteomalacia and in evaluating the severity of these conditions in individual subjects. Methods for these determinations are well known.[126]

In nutrition surveys, particularly of adults, estimation of the calcium content of blood has not appeared to be worth while in the United States or Europe. Calcium deficiency of sufficient degree to produce changes in the blood is uncommon in these areas and interpretation of borderline findings in older children or in adults is extremely difficult. In studies of infants, or in certain adult populations in the Far East, estimation of the level of blood calcium may be a valuable part of survey technics.

The normal concentration of calcium in the blood ranges from 9 to 11 mg. per 100 cc. in adults[111] and from 10 to 11 mg. per 100 cc. in children.[83] Macy[126] found average values for calcium and phosphorous of 10.4 and 5.6 mg. per 100 cc. respectively in a group of children 5 to 12 years of age. If serum calcium falls to low levels, the clinical syndrome of tetany or osteomalacia occurs.

OTHER TESTS

Routine Urinalysis

In studies of population groups, routine urinalysis should be carried out whenever possible, including determination of specific gravity, qualitative tests for albumin and sugar, and microscopic examination of the sediment. The information obtained will assist in detecting medical defects which may be responsible for malnutrition and which may explain loss of weight, hypoproteinemia, anemia, and other findings in certain members of the group examined.

Ketone Bodies in Urine and Blood

In certain surveys, it may be desirable to test for depletion of water and salt and to determine whether or not ketosis is present. An increase in blood ketones and ketonuria occur in a number of disease states including complete and partial starvation. In childhood particularly, even short periods of inadequate carbohydrate intake may lead to ketosis.[60] Problems of ketosis in relation to physical performance and diet have been discussed by Keys.[100] Analysis of urine for the presence of acetone bodies is a simple procedure which can readily be included in surveys of severely malnourished populations.[89, 94]

Chlorides in Urine and Blood

Water and salt deficiency are important problems in hot environments, especially in persons engaged in heavy labor. Dill[48] has shown that water expenditure may amount to 8 to 10 liters in twenty-four hours. A large part of the water loss is composed of sweat which also removes sodium and chloride from the body and rapid dehydration may develop. Problems of electrolyte balance may be further complicated if vomiting or diarrhea occurs. Mariott[129] has emphasized that differentiation should be made between pure water depletion, pure salt depletion, and mixed depletion of both water and salt. Such differentiation is vitally important in evaluation of the water and electrolyte balance of individuals but is difficult to accomplish in surveys. Since combined depletion or pure salt deficiency are the common findings, the procedures of most value in surveys are the detection of hemoconcentration and the determination of plasma and urine chlorides.

Dehydration is suggested by a concentration of serum protein above 7.5 Gm. per 100 cc. of blood[93] or by an increase in the volume of erythrocytes as measured by the hematocrit.[60] The concentration of hemoglobin may also be increased.

In salt deficiency there is a diminution or absence of chlorides in the urine.[129] A simple procedure for determination of urine chloride is that of Fantus,[129] or the method of Harvey has proved satisfactory.[129] Johnson has suggested that a urine chloride of less than 0.2 Gm. of sodium chloride per hour, or a fasting serum chloride of less than 98 milliequivalents per liter, is chemical evidence of salt deficiency. Talbott[205] considers that 100 milliequivalents per liter is the minimum normal concentration of serum chloride. In a study of persons with heat cramps, he found that the concentration of chloride in the urine was usually below 40 milliequivalents per liter. Marriott[129] has pointed out that the levels of chloride or sodium in the serum may not give accurate information as to the loss of sodium chloride from the body in states of mixed depletion where the loss of water is greater than that of salt. Detailed discussion of water and salt deficiency and of electrolyte balance may be found in several excellent reviews.[60, 129, 205]

In a survey of troops in Southeast Asia, Kark *et al.*[99] found satisfactory levels of urinary and serum chlorides especially in units who salted their water or their atta. In certain hard-working units, however, where the importance of salt was either unrecognized or ignored, low serum chloride concentrations and low urinary chlorides were observed. Collapse and abdominal and muscular cramps were reported to have occurred in these units.

SUMMARY

Considerable progress has been made in the biochemical evaluation of nutritional status. Tests have been devised which are indicative of the previous dietary intake of nutrients, methods are available for estimating saturation or depletion of bodily stores of certain chemical substances, and there are a few tests which measure the metabolically active forms of dietary essentials and the abnormalities which occur in deficiency disease. Although exact criteria for the interpretation of findings in terms of deficient, adequate, or optimal nutrition are lacking in most instances, chemical tests are a valuable part of survey technics in obtaining a general picture of the nutritional level of population groups. Findings should be reported in terms of actual figures obtained, or in the form of distribution curves, rather than as deviations from a mean. This will permit reinterpretation of data when more accurate criteria for evaluation are available.

The use of micromethods has greatly facilitated the application of chemical tests to mass examination and should assist in solving many existing problems. New tests are needed and experiments under carefully controlled conditions, with existing methods, should yield valuable data. In the future, biochemical examination will undoubtedly be an integral part of all nutrition surveys.

TESTS WHICH MAY BE USEFUL IN NUTRITION SURVEYS

1. *Serum Proteins:*
    Micro-Kjeldahl titration or nesslerization[175]
    Specific gravity-copper sulphate,[177] falling drop,[9] micromethod[123]
2. *Hemoglobin and Iron:*
    Oxyhemoglobin-macromethod[214] or micromethod[15]
    Alkaline hematin[104]
    Copper sulphate[177]
    Serum iron[33, 149, 194]
3. *Vitamin A in Blood:*
    Macromethods, Carr-Price reaction,[36, 42, 103, 132] micromethod[18]
4. *Thiamine in Urine:*
    One-hour fasting excretion and load tests (oral or parenteral)
    Thiochrome procedure[169, 74, 131]
    Pyramine and thiamine determination[142]
5. *Riboflavin:*
    a. Urinary excretion—one-hour fasting and load tests (oral or parenteral)
        Microbiologic method[198]

Fluorometric procedures[38, 75]
Direct fluorometric method after load tests[55, 89, 94]
b. In erythrocytes[15, 28]

6. *Niacin:*
One-hour fasting excretion and load tests
Determination of N^1-methylnicotinamide[85, 86, 158]

7. *Ascorbic Acid:*
In blood-plasma and leukocytes
Macromethods,[11, 30, 148, 182, 183] micromethod[17]
One-hour fasting urinary excretion[10, 92]
Load test: estimation of blood concentration[98]
Load tests: urinary excretion-oral test dose,[52, 91, 93] parenteral test dose[215]

8. *Vitamin D:*
Phosphatase, macromethod,[21, 22] micromethod[16]

BIBLIOGRAPHY

1. Abels, J. C., Gorham, A. T., Pack, G. T., and Rhoads, C. P. Metabolic studies in patients with cancer of the gastro-intestinal tract. *J. Clin. Investigation* 20:749, 1941.
2. Adamson, J. D., Jolliffe, N., Kruse, H. D., Lowry, O. H., Moore, P. E., Platt, B. S., Sebrell, W. H., Tice, J. W., Tisdall, F. F., Wilder, R. M., and Zamecnik, P. C. Medical survey of nutrition in Newfoundland. *Canad. M. A. J.* 52:227, 1945.
3. Anderson, R. K., Calvo, J., Serrano, G., and Payne, G. C. A study of the nutritional status and food habits of Otomi indians in the Mezquital valley of Mexico. *Am. J. Pub. Health* 36:883, 1946.
4. Anderson, R. K., and Milam, D. F. Biomicroscopy of the eyes in evaluation of nutritional status. Conjunctival changes. *J. Nutrition* 30:11, 1945.
5. Aron, H. C. S., Craig, R. M., Farmer, C. J., Kendell, H. W., and Schwemlein, G. X. Effect of elevated body temperature on plasma vitamin A and carotene. *Proc. Soc. Exper. Biol. & Med.* 61:271, 1946.
6. Atchley, J., Bacon, R., Curran, G., and Kirk, D. A clinical evaluation of the copper sulfate method for measuring specific gravities of whole blood and plasma. *J. Lab. & Clin. Med.* 30:830, 1945.
7. Axelrod, A. E., Gordon, A. S., and Elvehjem, C. A. The relationship of the dietary intake of nicotinic acid to the coenzyme I content of blood. *Am. J. M. Sc.* 199:697, 1940.
8. Axelrod, A. E., Spies, T. D., and Elvehjem, C. A. Riboflavin content of blood and muscle in normal and in malnourished humans. *Proc. Soc. Exper. Biol. & Med.* 46:146, 1941.
9. Barbour, H. G., and Hamilton, W. F. The falling drop method for determining specific gravity. *J. Biol. Chem.* 69:625, 1926.

10. Berryman, G. H., Henderson, C. R., Wheeler, N. C., Cogswell, R. C., Jr., Spinella, J. R., Grundy, W. E., Johnson, H. W., Wood, M. E., Denko, C. W., Friedemann, T. E., Harris, S. C., Ivy, A. C., and Youmans, J. B. Effects in young men consuming restricted quantities of B-complex vitamins and protein and changes associated with supplementation. *Am. J. Physiol.* 148:618, 1947.
11. Bessey, O. A. A method for the determination of small quantities of ascorbic acid and dehydroascorbic acid in turbid and colored solutions in the presence of other reducing substances. *J. Biol. Chem.* 126:771, 1938.
12. Bessey, O. A. Personal Communication, 1946.
13. Bessey, O. A. To be published.
14. Bessey, O. A., and King, C. J. The distribution of vitamin C in plant and animal tissues, and its determination. *J. Biol. Chem.* 103:687, 1933
15. Bessey, O. A., and Lowry, O. H. Biochemical methods in nutritional surveys. *Am. J. Pub. Health* 35:941, 1945.
16. Bessey, O. A., Lowry, O. H., and Brock, M. J. A method for the rapid determination of alkaline phosphatase with five cubic millimeters of serum. *J. Biol. Chem.* 164:321, 1946.
17. Bessey, O. A., Lowry, O. H., and Brock, M. J. The quantitative determination of ascorbic acid in small amounts of white blood cells and platelets. *J. Biol. Chem.* 168:197, 1947.
18. Bessey, O. A., Lowry, O. H., Brock, M. J., and Lopez, J. A. The determination of vitamin A and carotene in small quantities of blood serum. *J. Biol. Chem.* 166:177, 1946.
19. Biological Symposia, Vol. XII. Lancaster, Pa., Cattell, 1947.
20. Blum, L. L. The photoelectric determination of erythrocyte count. *Am. J. Clin. Path.*, Tech. Section, 9:85, 1945.
21. Bodansky, A. Phosphatase studies. *J. Biol. Chem.* 101:93, 1933.
22. Bodansky, A. Determination of serum inorganic phosphate and serum phosphatase. *Am. J. Clin. Path.*, Tech. Suppl. 1:51, 1937.
23. Bodansky, A., and Jaffe, H. L. Phosphatase studies. *Arch. Int. Med.* 54:88, 1934.
24. Bodansky, A., and Jaffe, H. L. Phosphatase studies. *Am. J. Dis. Child.* 48:1268, 1934.
25. Bradford, E. A. M., and Coke, H. The microbiological determination of riboflavin in blood. *Biochem. J.* 39:379, 1945.
26. Brewer, W., Porter, T., Ingalls, R., and Ohlson, M. A. The urinary excretion of riboflavin by college women. *J. Nutrition* 32:583, 1946.
27. Bueding, E., and Wortis, H. The stabilization and determination of pyruvic acid in the blood. *J. Biol. Chem.* 133:585, 1940.
28. Burch, H. B., Bessey, O. A., and Lowry, O. H. Fluorometric measurement of riboflavin and its natural derivatives in small quantities of blood serum and cells. *J. Biol. Chem.* 175:457, 1948.

29. Burger, G. C. E., Sandstead, H. R., and Drummond, J. C. Starvation in Western Holland, 1945. *Lancet* 2:282, 1945.

30. Butler, A. M., Cushman, M., and McLachlan, E. A. The determination of ascorbic acid in whole blood and its constituents by means of methylene blue; macro- and micro-methods. *J. Biol. Chem.* 150:453, 1943.

31. Campbell, W. R., and Hanna, M. I. Sulfites as protein precipitates. *J. Biol. Chem.* 119:9, 1937.

32. Carter, C. W., and O'Brien, J. R. P. The nicotinic acid content of blood in health and disease. *Quart. J. Med.* 14:197, 1945.

33. Cartwright, G. E., Lawritsen, M. A., Jones, P. J., Merrill, I. M., and Wintrobe, M. M. The anemia of infection. *J. Clin. Investigation* 25:65, 1946.

34. Cartwright, G. E., and Wintrobe, M. M. Hematologic survey of repatriated American military personnel. *J. Lab. & Clin. Med.* 31:886, 1946.

35. Cayer, D., and Cody, S. The nutritional state of patients with peptic ulcer as measured by vitamin levels. *Gastroenterology* 9:54, 1947.

36. Clausen, S. W., and McCoord, A. B. The carotinoids and vitamin A of the blood. *J. Pediat.* 13:635, 1938.

37. Cogswell, R. C., Berryman, G. H., Henderson, C. R., Denko, C. W., Spinella, J. R., Friedemann, T. E., Ivy, A. C., and Youmans, J. B. Absence of rapid deterioration in moderately active young men on a restricted intake of B-complex vitamins and animal protein. *Am. J. Physiol.* 147:39, 1946.

38. Conner, R. T., and Straub, G. J. Combined determination of riboflavin and thiamine in food products. *Indust. & Engin. Chem.* (Anal. Ed.) 13:385, 1941.

39. Coulson, R. A., Ellinger, P., and Smart, G. A. The urinary elimination of nicotinamide methochloride in subjects with normal gums and with acute and chronic gingivitis. *Brit. M. J.* 1:6, 1945.

40. Crandon, J. H., Lund, C. C., and Dill, D. B. Experimental human scurvy. *New England J. Med.* 223:353, 1940.

41. Dann, W. J., and Darby, W. J. The appraisal of nutritional status (nutriture) in humans. *Physiol. Rev.* 25:326, 1945.

42. Dann, W. J., and Evelyn, K. A. The determination of vitamin A with the photoelectric colorimeter. *Biochem. J.* 32:1008, 1938.

43. Darby, W. J., Hahn, P. F., Kaser, M. M., Steinkamp, R. C., Densen, P. M., and Cook, M. B. The absorption of radioactive iron by children 7-10 years of age. *J. Nutrition* 33:107, 1947.

44. Darby, W. J., and Milam, D. F. Field study of the prevalence of the clinical manifestations of dietary inadequacy. *Am. J. Pub. Health* 35:1014, 1945.

45. Davidson, L. S. P., Donaldson, G. M. M., Lindsay, S. T., and Roscoe, M. H. Nutritional iron deficiency anemia in wartime. *Brit. M. J.* 2:333, 1944.

46. Davis, M. V., Oldham, H. G., and Roberts, L. J. Riboflavin excretions of young women on diets containing varying levels of B vitamins. *J. Nutrition* 32:143, 1946.
47. Denko, C. W., Grundy, W. E., Potter, J. W., and Berryman, G. H. The excretion of B-complex vitamins in the urine and feces of seven normal adults. *Arch. Biochem.* 10:33, 1946.
48. Dill, D. B. Life, Heat and Altitude. Cambridge, Mass., Harvard, 1938.
49. Dodds, M. L., and MacLeod, F. L. Blood plasma ascorbic acid levels on controlled intakes of ascorbic acid. *Science* 106:67, 1947.
50. Dogramaci, I. Scurvy: A survey of 241 cases. *New England J. Med.* 235:185, 1946.
51. Evelyn, K. A. A stabilized photoelectric colorimeter with light filters. *J. Biol. Chem.* 115:63, 1936.
52. Farmer, C. J. Some aspects of vitamin C metabolism. *Federation Proc.* 3:179, 1944.
53. Farmer, C. J., and Abt, A. F. Determination of reduced ascorbic acid in small amounts of blood. *Proc. Soc. Exper. Biol. & Med.* 34:146, 1936.
54. Feder, V., Lewis, G. T., and Alden, H. S. Studies on the urinary excretion of riboflavin. *J. Nutrition* 27:347, 1944.
55. Ferrebee, J. W. The urinary excretion of riboflavin. Fluorometric methods for its estimation. *J. Clin. Investigation* 19:251, 1940.
56. Field, H., Jr., Melnick, D., Robinson, W. D., and Wilkinson, C. F., Jr. Studies on the clinical diagnosis of pellagra (nicotinic acid deficiency). *J. Clin. Investigation* 20:379, 1941.
57. Foltz, E. E., Barborka, C. J., and Ivy, A. C. The level of vitamin B-complex in the diet at which detectable symptoms of deficiency occur in man. *Gastroenterology* 2:323, 1944.
58. Friedemann, T. E., Haugen, G. E., and Kmieciak, T. C. Pyruvic acid. *J. Biol. Chem.* 157:673, 1945.
59. Fullerton, H. W., Mair, M. I., and Unsworth, P. A survey of the haemoglobin levels of the poor classes in Aberdeen. *Brit. M. J.* 2:373, 1944.
60. Gamble, J. L. Chemical Anatomy, Physiology and Pathology of Extra Cellular Fluid. (Ed. 4) Cambridge, Mass., Harvard, 1942.
61. Goldsmith, G. A. Urinary excretion of nicotinic acid and its derivatives. *Arch. Int. Med.* 73:410, 1944.
62. Goldsmith, G. A., and Fontnote, A. The blood lactate—pyruvate relationship in various physiologic and pathologic states. *Am. J. M. Sc.* 215:182, 1948.
63. Goldsmith, G. A., and Sarett, H. P. Unpublished Data.
64. Goodhart, R., and Sinclair, H. M. The estimation of cocarboxylase (vitamin B_1 diphosphate ester) in blood. *Biochem. J.* 33:1099, 1939; Deficiency of vitamin B_1 in man as determined by blood cocarboxylase. *J. Biol. Chem.* 132:11, 1940.

65. Greenberg, L. D., and Rinehart, J. F. Methods for determination of thiamine in blood and tissues with observations on relative contents. *Proc. Soc. Exper. Biol. & Med.* 59:9, 1945.

66. Grifft, H. H., and Hauck, H. M. A comparison of four methods for studying the urinary excretion of thiamine. *J. Nutrition* 31:635, 1946.

67. Hagedorn, D. R., Kyhos, E., Germek, D. A., and Severinghaus, E. L. Observations on riboflavin excretion by the adult male. *J. Nutrition* 29:179, 1945.

68. Haines, J. E., Klosterman, A. M., Hauck, H. M., Delaney, M. A., Kline, A. B., Sisler, E. B., and Newell, M. Tissue reserves of ascorbic acid in normal adults on three levels of intake. *J. Nutrition* 33:479, 1947.

69. Harris, P. L., Hickman, K. C. D., Jensen, J. L., and Spies, T. D. Survey of the blood plasma levels of vitamin A, carotene, ascorbic acid and tocopherols in an area of endemic malnutrition. *Am. J. Pub. Health* 36:155, 1946.

70. Harris, L. J., and Ray, S. M. Specificity of hexuronic (ascorbic) acid as anti-scorbutic factor. *Biochem. J.* 27:580, 1933.

71. Hathaway, M. L., and Lobb, D. E. A comparison of riboflavin synthesis and excretion in human subjects on synthetic and natural diets. *J. Nutrition* 32:9, 1946.

72. Hegsted, D. M., Tsongas, A. G., Abbott, D. B., and Stare, F. J. Protein requirement of adults. *J. Lab. & Clin. Med.* 31:261, 1946.

73. Hennessy, D. J. Biological Symposia, Vol. XII, pp. 86–120B. Lancaster, Pa., Cattell, 1947.

74. Hennessy, D. J., and Cerecedo, L. R. The determination of free and phosphorylated thiamine by a modified thiochrome assay. *J. Am. Chem. Soc.* 61:179, 1939.

75. Hodson, A. Z., and Norris, L. C. A fluorometric method for determining the riboflavin content of foodstuffs. *J. Biol. Chem.* 131:621, 1931.

76. Holland, A. H., Jr., Canniff, J. C., and Bruger, M. Evaluation of the vitamin C status of human subjects: Studies with intradermal dye discoloration, capillary fragility, fasting plasma vitamin C level and vitamin C saturation. *J. Lab. & Clin. Med.* 32:124, 1947.

77. Holt, L. E., Jr. The B vitamins and certain problems they present to the practicing physician. *Pennsylvania M. J.* 46:451, 1943.

78. Holt, L. E., Jr. The thiamine requirement of man. *Federation Proc.* 3:171, 1944.

79. Holt, L. E., Jr. Exhibit, New York Academy of Medicine Graduate Fortnight, October, 1947.

80. Holt, L. E., Jr., and Najjar, V. A. A simple method for the laboratory diagnosis of subclinical deficiencies of thiamine, riboflavin, and nicotinic acid. *Bull. Johns Hopkins Hosp.* 70:329, 1942.

81. Horecker, B. L. A primary standard for the colorimetric determination of hemoglobin. *J. Lab & Clin. Med.* 31:589, 1946.

82. Hou, H. C., and Dju, M. Y. Riboflavin deficiency among Chinese. *Chinese M. J.* 62:140, 1944.

83. Howland, J., and Kramer, B. Calcium and phosphorus in the serum in relation to rickets. *Am. J. Dis. Child.* 22:105, 1921.

84. Hsu, H. C. Serum carotenoids and vitamin A in Chinese. *Chinese M. J.* 61:238, 1943.

85. Huff, J. W., and Perlzweig, W. A. A rapid method of estimating N^1-methylnicotinamide in urine. *J. Biol. Chem.* 150:483, 1943.

86. Huff, J. W., Perlzweig, W. A., and Tilden, M. W. A simple method for the determination of N^1-methylnicotinamide in urine. *Federation Proc.* 4:92, 1945.

87. Hulse, M. C., Weissman, N., Stotz, E., Clinton, M., and Ferrebee, J. W. Subclinical vitamin deficiency. *Ann. Int. Med.* 21:440, 1944.

88. Inadequate diets and nutritional deficiencies in the United States. Bulletin No. 109, pp. 1-56. Washington, D. C., National Research Council, 1943.

89. Johnson, R. E. A field nutritional laboratory. *War Med.* 7:222, 1945.

90. Johnson, R. E., Contreras, L. A., Consolazio, F. C., and Robinson, P. F. A comparison of intravenous and oral vitamin tolerance tests. *Am. J. Physiol.* 144:58, 1945.

91. Johnson, R. E., Darling, R. C., Sargent, F., and Robinson, P. F. Effects of variations in dietary vitamin C on the physical well being of manual workers. *J. Nutrition* 29:155, 1945.

92. Johnson, R. E., Henderson, C. R., Robinson, P. F., and Consolazio, F. C. Comparative merits of fasting specimens, random specimens and oral loading tests on field nutritional surveys. *J. Nutrition* 30:89, 1945.

93. Johnson, R. E., Sargent, F., Robinson, P. F., and Consolazio, F. C. Assessment of nutritional and metabolic condition in the field. *War Med.* 7:227, 1945.

94. Johnson, R. E., Sargent, F., Robinson, P. F., and Consolazio, F. C. Estimation of riboflavin, thiamine and N^1-methylnicotanimide. Rapid field methods. *Indust. & Engin. Chem.* (Anal. Ed.) 17:384, 1945.

95. Johnstone, W. M., Drake, T. G. H., Tisdall, F. F., and Harvie, F. A. A study of the ascorbic acid metabolism of healthy young Canadians. *Canad. M. A. J.* 55:581, 1946.

96. Jolliffe, N. Am. Pub. Health Assn. Meeting, October 6-10, 1947.

97. Kagan, B. M. A simple method for the estimation of total protein content of plasma and serum. *J. Clin. Investigation* 17:369,1938.

98. Kajdi, L., Light, J., and Kajdi, C. A test for the determination of vitamin C storage. Vitamin C index. *J. Pediat.* 15:197, 1939.

99. Kark, L. M., Aiton, H. F., Pease, E. D., Bean, W. B., Henderson, C. R., Johnson, R. E., and Richardson, L. M. Tropical deterioration and nutrition. Clinical and biochemical observations on troops. *Medicine* 26:1, 1947.

100. Keys, A. Physical performance in relation to diet. *Federation Proc.* 2:164, 1943.

101. Keys, A., Henschel, A., Taylor, H. L., Mickelsen, O., and Brozek, J. Experimental studies on man with a restricted intake of the B vitamins. *Am. J. Physiol.* 144:5, 1945.

102. Keys, A., Taylor, H. L., Mickelsen, O., and Henschel, A. Famine edema and the mechanism of its formation. *Science* 103:669, 1946.

103. Kimble, M. S. The photocolorimetric determination of vitamin A and carotene in human plasma. *J. Lab. & Clin. Med.* 24:1055, 1938-39.

104. King, E. J., Gilchrist, M., and Delory, G. E. Accuracy of haemoglobin methods. *Lancet* 1:239, 1944.

105. King, E. J., Gilchrist, M., and Matheson, A. The haemoglobin equivalent of the B. S. I. Haldane Standard. *Brit. M. J.* 1:250, 1944.

106. Klasmer, R. Serum phosphatase activity and clinical rickets in children in Jerusalem. *Am. J. Dis. Child.* 67:348, 1944.

107. Klein, J. R., Perlzweig, W. A., and Handler, P. Determination of nicotinic acid in blood cells and plasma. *J. Biol. Chem.* 145:27, 1942.

108. Knox, W. E. A.A.A.S. Conference, New London, New Hampshire, 1947.

109. Knox, W. E., and Grossman, W. I. A new metabolite of nicotinamide. *J. Biol. Chem.* 166:391, 1946.

110. Kohn, H. I., and Bernheim, F. The blood V-factor (coenzyme) level in normal and pathological subjects. *J. Clin. Investigation* 18:585, 1939.

111. Kolmer, J. A. Clinical Diagnosis by Laboratory Examination. (Ed. 1, Rev.) p. 132. New York, Appleton, 1944.

112. Krause, R. F., and Pierce, H. B. Blood levels and absorption of vitamin A in children with keratosis follicularis. *J. Nutr.* 33:633, 1947.

113. Krehl, W. H., Strong, F. M., and Elvehjem, C. A. Determination of nicotinic acid: Modifications in microbiological methods. *Indust. & Engin. Chem.* (Anal. Ed.) 15:471, 1943.

114. Kruse, H. D. A concept of the deficiency states. *Milbank Mem. Fund. Quart.* 20:245, 1942.

115. Kyhos, E. D., Gordon, E. S., Kimble, M. S., and Sevringhaus, E. L. The minimum ascorbic acid need of adults. *J. Nutrition* 27:271, 1944.

116. Leeson, H. J., Webb, J. F., Ferguson, H. P., Semmons, E. M., and McHenry, E. W. A study of ascorbic acid nutrition. *Canad. M. A. J.* 53:341, 1945.

117. Lerner, A. B., and Barnum, C. P. A new rapid method for the determination of serum albumin and globulin by ultraviolet absorption. *Arch. Biochem.* 11:505, 1946.

118. Lewis, J. M., Bodansky, O., Lillienfield, M. C. C., and Schneider, H. Supplements of vitamins A and of carotene during pregnancy. Their

effect on the levels of vitamin A and carotene in the blood of mother and newborn infant. *Am. J. Dis. Child.* 73:143, 1947.

119. LINGHORNE, W. J., MCINTOSH, W. G., TICE, J. W., TISDALL, F. F., MCCREARY, J. F., DRAKE, T. G. H., GREAVES, A. V., and JOHNSTONE, W. M. Relation of ascorbic acid intake to gingivitis. *Canad. M. A. J.* 54:105, 1946.
120. LIPSCOMB, F. M. Medical aspects of Blesen concentration camp. *Lancet* 2:313, 1945.
121. LOWRY, O. H., and BESSEY, O. A. Microchemical methods for nutritional studies. *Federation Proc.* 4:268, 1945.
122. LOWRY, O. H., BESSEY, O. A., BROCK, M. J., and LOPEZ, J. A. The interrelationship of dietary, serum, white blood cell and total body ascorbic acid. *J. Biol. Chem.* 166:111, 1946.
123. LOWRY, O. H., and HUNTER, T. H. The determination of serum protein concentration with a gradient tube. *J. Biol. Chem.* 159:465, 1945.
124. MCMILLIAN, R. B., and INGLIS, J. C. Scurvy: A survey of fifty-three cases. *Brit. M. J.* 2:233, 1944.
125. MCNEE, G. Z. I., and REID, J. Vitamin C nutrition in the Royal Navy and in a section of the civilian population during war time. *Lancet* 2:538, 1942.
126. MACY, I. G. Nutrition and Chemical Growth in Childhood. (Vol. I) Springfield, Illinois, Thomas, 1946, pp. 212, 314, 316.
127. MACY, I. G. Nutrition and Chemical Growth in Childhood. (Vol. II) Springfield, Illinois, Thomas, 1946.
128. MADDEN, S. C., and WHIPPLE, G. H. Plasma proteins. Their sources, production and utilization. *Physiol. Rev.* 20:194, 1940.
129. MARRIOTT, H. L. Water and salt depletion. *Brit. M. J.* 1:245, 285, 328, 1947.
130. MASON, H. L., and WILLIAMS, R. D. The urinary excretion of thiamine as an index of the nutritional level. Assessment of the value of a test dose. *J. Clin. Investigation* 21:247, 1942.
131. MASON, H. L., and WILLIAMS, R. D. Determination of thiamine in urine by the thiochrome method: Estimation of the blank. *J. Biol. Chem.* 146:589, 1942.
132. MAY, C. D., BLACKFAN, K. D., MCCREARY, J. F., and ALLEN, F. H., JR. Clinical studies of vitamin A in infants and children. *Am. J. Dis. Child.* 59:1167, 1940.
133. MELNICK, D. Vitamin B_1 (thiamine) requirement of man. *J. Nutrition* 24:139, 1942.
134. MELNICK, D., and FIELD, H., JR. Clinical determination of vitamin B_1. *J. Biol. Chem.* 127:505, 515, 531, 1939.
135. MELNICK, D., and FIELD, H., JR. Determination of nicotinic acid in biological materials by means of photoelectric colorimetry. *J. Biol. Chem.* 134:1, 1940.
136. MELNICK, D., and FIELD, H., JR. Chemical determination of nicotinic acid: Inhibitory effect of cyanogen bromide upon the aniline side reactions. *J. Biol. Chem.* 135:53, 1940.

137. Melnick, D., and Field, H., Jr. Thiamine clearance as an index of nutritional status. *J. Nutrition* 24:131, 1942.

138. Metcoff, J., Favour, C. B., and Stare, F. J. Plasma protein and hemoglobin in the protein deficient rat. A three dimensional study. *J. Clin. Investigation* 24:82, 1946.

139. Metcoff, J., Goldsmith, G. A., McQueeney, A. J., Dove, R. F., McDevitt, E., Dove, M. A., and Stare, F. J. Nutritional survey in Norris Point, Newfoundland. *J. Lab. & Clin. Med.* 30:475, 1945.

140. Methods of Vitamin Assay. New York, Interscience, 1947.

141. Mickelsen, O., Caster, W. O., and Keys, A. A statistical evaluation of the thiamine and pyramin excretion of normal young men on controlled intakes of thiamine. *J. Biol. Chem.* 168:415, 1947.

142. Mickelsen, O., Condiff, H., and Keys, A. The determination of thiamine in urine by means of the thiochrome technique. *J. Biol. Chem.* 160:351, 1945.

143. Mickelsen, O., and Erickson, L. L. The F_2 excretion of normal young men on different levels of niacin intake. *Proc. Soc. Exper. Biol. & Med.* 58:33, 1945.

144. Milam, D. F. Plasma protein levels in normal individuals. *J. Lab. & Clin. Med.* 31:285, 1946.

145. Milam, D. F., and Anderson, R. K. Nutrition survey of an entire rural county in North Carolina. *South. M. J.* 37:597, 1944.

146. Milam, D. F., and Muench, H. Hemoglobin levels in specific race, age and sex groups of a normal North Carolina population. *J. Lab. & Clin. Med.* 31:878, 1946.

147. Milam, D. F., and Wilkins, W. Vitamin C in normal nutrition (effect of low cost diet on plasma levels over a six weeks period). *South. Med. and Surg.* 104:191, 1942.

148. Mindlin, R. L., and Butler, A. M. The determination of ascorbic acid in plasma; a macromethod and micromethod. *J. Biol. Chem.* 122:673, 1937-38.

149. Moore, C. V., Arrowsmith, W. R., Welch, J., and Minnich, V. Studies in iron transportation and metabolism. *J. Clin. Investigation* 18:553, 1939.

150. Munks, B., Kaucher, M., Moyer, E. Z., Harris, M. E., and Macy, I. G. Metabolism of women during reproductive cycle. *J. Nutrition* 33:601, 1947.

151. Najjar, V. A. The fluorometric determination of riboflavin in urine and other biological fluids. *J. Biol. Chem.* 141:355, 1941.

152. Najjar, V. A. The laboratory diagnosis of nicotinic acid deficiency. An improved procedure for the determination of F_2 (N^1-methyl nicotinamide derivative) in the urine. *Bull. Johns Hopkins Hosp.* 74:392, 1944.

153. Najjar, V. A., and Holt, L. E. Jr. The excretion of specific fluorescent substances in the urine in pellagra. *Science* 93:20, 1941.

154. NAJJAR, V. A., and HOLT, L. E. JR. A simple method for the laboratory diagnosis of subclinical deficiencies of thiamine, riboflavin and nicotinic acid (demonstration) *Federation Proc.* 1:117, 1942.

155. NAJJAR, V. A., and HOLT, L. E., JR. Clinical diagnosis of deficiencies of thiamine, riboflavin and niacin. *Journal-Lancet* 63:366, 1943.

156. NAJJAR, V. A., HOLT, L. E., JR., STEIN, H. J., and KABLER, C. U. The excretion of specific fluorescent substances in the urine in experimental nicotinic acid deficiencies. *J. Clin. Investigation* 21:263, 1942.

157. NAJJAR, V. A., and KETRON, K. C. An improved thiochrome method for the determination of thiamine in urine. *J. Biol. Chem.* 152:597, 1944.

158. NAJJAR, V. A., and WOOD, R. W. Presence of a hitherto unrecognized nicotinic acid derivative in human urine. *Proc. Soc. Exper. Biol. & Med.* 44:386, 1940.

159. Nutritional status of a population group in Madrid. *Nutrition Rev.* 1:231, 1943.

160. The nutritional situation in internment camps in France. *Nutrition Rev.* 2:205, 1944.

161. A survey of hemoglobin levels in Great Britain in 1943. *Nutrition Rev.* 4:154, 1946.

162. Present knowledge of ascorbic acid (vitamin C) in nutrition. *Nutrition Rev.* 4:259, 1946.

163. OLDHAM, H. G., DAVIS, M. V., and ROBERTS, L. J. Thiamine excretions and blood levels of young women on diets containing varying levels of the B vitamins with some observations on niacin and pantothenic acid. *J. Nutrition* 32:163, 1946.

164. OLDHAM, H. G., ROBERTS, L. J., and YOUNG, M. Results of providing a liberally adequate diet to children in an institution. *J. Pediat.* 27:418, 1945.

165. OLHSON, M. A., CEDERQUIST, O., DONELSON, E. G., LEVERTON, R. M., LEWIS, G. K., HIMWICH, W. A., and REYNOLDS, M. S. Hemoglobin concentrations, red cell counts and erythrocyte volumes of college women of the North Central States. *Am. J. Physiol.* 142:727, 1944.

166. PAPAGEORGE, E., and LEWIS, G. T. A study of the fasting-hour excretion of thiamine in the urine of normal subjects. *J. Nutrition* 34:301, 1947.

167. PEDLEY, F. G. Hemoglobin concentration in college women. *Canad. M. A. J.* 51:351, 1944.

168. PERLZWEIG, W. A., HUFF, J. A., and GUE, I. The excretion of thiamine, riboflavin and nicotinic acid by fasting men. *Federation Proc.* 3:62, 1944.

169. PERLZWEIG, W. A., KAMIN, H., GUE, I., and BLALOCK, J. B. A modification of the thiochrome method for the rapid determination of thiamine in urine. *Arch. Biochem.* 6:97, 1945.

170. PERLZWEIG, W. A., LEVY, E. D., and SARETT, H. P. Nicotinic acid derivatives in human urine and their determinations. *J. Biol. Chem.* 136:729, 1940.

171. Perlzweig, W. A., Rosen, F., Levitas, N., and Robinson, J. The excretion of nicotinic acid derivatives after ingestion of tryptophane by man. *J. Biol. Chem.* 167:511, 1947.

172. Perlzweig, W. A., and Sarett, H. P. Unpublished data.

173. Perlzweig, W. A., Sarett, H. P., and Margolis, L. A. Studies in nicotinic acid metabolism. *J.A.M.A.* 118:28, 1942.

174. Peters, J. P., and Eisenman, A. J. The serum proteins in diseases not primarily affecting the cardiovascular system or kidneys. *Am. J. M. Sc.* 186:808, 1933.

175. Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry. (Vol. II.) Baltimore, Williams and Wilkins, 1932.

176. Pett, L. B. Errors in applying nutrient allowances to dietary surveys or food policies. *Canad. J. Pub. Health* 36:69, 1945.

177. Phillips, R. A., Van Slyke, D. D., Dole, V. P., Emerson, K., Jr., Hamilton, P. B., and Archibald, R. M. Copper sulfate method for measuring specific gravities of whole blood and plasma, with line charts for calculating plasma proteins, hemoglobin, and hematocrit from plasma and whole blood gravities. *Bull. U. S. Army M. Dept.* 71:66, 1943.

178. Popper, H. Distribution of vitamin A in tissue as visualized by fluorescence microscopy. *Physiol. Rev.* 24:205, 1944.

179. Robinson, H. W., Price, J. W., and Hogden, C. G. The estimation of albumin and globulin in blood serum. *J. Biol. Chem.* 120:481, 1937.

180. Robinson, H. W., Price, J. W., and Hogden, C. G. The estimation of albumin and globulin in blood serum. *J. Biol. Chem.* 126:207, 1938.

181. Robinson, H. W., Price, J. W., and Hogden, C. G. The estimation of albumin and globulin in blood serum. *J. Biol. Chem.* 126:213, 1938.

182. Robinson, W. B., and Stotz, E. The indophenol-xylene extraction method for ascorbic acid and modifications for interfering substances. *J. Biol. Chem.* 160:217, 1945.

183. Roe, J. H., and Oesterling, M. J. The determination of dehydroascorbic acid and ascorbic acid in plant tissues by the 2, 4-dinitrophenylhydrazine method. *J. Biol. Chem.* 152:511, 1944.

184. Rosen, F., Perlzweig, W. A., and Handler, P. A fluorimetric assay for N^1-methyl-6-pyridone-3-carboxylamide. *Federation. Proc.* 7:181, 1948.

185. Ruffin, J. M., Cayer, D., and Perlzweig, W. A. The relationship between the clinical picture of a mild or early vitamin deficiency and laboratory determinations of vitamin levels. *Gastroenterology* 3:340, 1944.

186. Sachar, L. A., Horvitz, A., and Elman, R. Studies on hypoalbuminemia produced by protein deficient diets. *J. Exper. Med.* 75:453, 1942.

187. Sarett, H. P., and Goldsmith, G. A. The effect of tryptophane on the excretion of nicotinic acid derivatives in humans. *J. Biol. Chem.* 167:293, 1947.

188. Sarett, H. P., and Goldsmith, G. A. Trytophane and nicotinic acid studies in man. *J. Biol. Chem.* 177:461, 1949.

189. Sarett, H. P., Huff, J. W., and Perlzweig, W. A. Studies in nicotinic acid metabolism. *J. Nutrition* 23:23, 1942.

190. Sarett, H. P., Klein, J. R., and Perlzweig, W. A. The effect of the level of protein intake upon urinary excretion of riboflavin and nicotinic acid in dogs and rats. *J. Nutrition* 24:295, 1942.

191. Sarett, H. P., and Perlzweig, W. A. The effect of protein and B-vitamin levels of the diet upon the tissue content and balance of riboflavin and nicotinic acid in rats. *J. Nutrition* 25:173, 1943.

192. Sargent, F., Robinson, P., and Johnson, R. E. F_1 and F_2 of Najjar and Holt in the urine of normal young men. *J. Clin. Investigation* 23:714, 1944.

193. Schultz, A. S., Atkins, L., and Frey, C. N. Determination of vitamin B_1 by yeast fermentation method. *Ind. Eng. Chem.* (Anal. Ed.) 14:35, 1942.

194. Shank, R. E. Am. Pub. Health Assn. Meeting, October 6-10, 1947.

195. Sinclair, H. M. Wartime nutrition in England as a Public Health problem. *Am. J. Pub. Health* 34:828, 1944.

196. Smith, S. L. Human requirements of vitamin C. *J.A.M.A.* 111:1753, 1938.

197. Smith, C., and Stuart, H. Am. Pub. Health Assn. Meeting, October 6-10, 1947.

198. Snell, E. E., and Strong, F. M. A microbiological assay for riboflavin. *Indust. & Engin. Chem.* (Anal. Ed.) 11:346, 1939.

199. Snell, E. E., and Wright, L. D. A microbiological method for the determination of nicotinic acid. *J. Biol. Chem.* 139:675, 1941.

200. Spector, S., McKhann, C. F., and Meserve, E. R. Effect of disease on nutrition. *Am. J. Dis. Child.* 66:376, 1943.

201. Stare, F. J., and Davidson, C. S. Protein: Its role in human nutrition. *J.A.M.A.* 127:985, 1945.

202. Stotz, E., and Bessey, O. A. The blood lactate-pyruvate relation and its use in experimental thiamine deficiency in pigeons. *J. Biol. Chem.* 143:625, 1942.

203. Strong, F. M., Feeney, R. E., Moore, B., and Parsons, H. T. The riboflavin content of blood and urine. *J. Biol. Chem.* 137:363, 1941.

204. Sure, B., and Ford, Z. W., Jr. Vitamin interrelationships. *J. Biol. Chem.* 146:241, 1942.

205. Talbott, J. H. Heat cramps. *Medicine* 14:323, 1935.

206. Thysell, T. C-Vitaminstandard und C-Hypovitaminose; Uber Kost, Blutascorbinsaure und Kapellarblutungsprobe. *Acta Paediat.* 26:481, 1939.

207. Tillmans, J., Hirsch, P., and Vaubel, R. Reducing power of plant foodstuffs and its relation to vitamin C. *Ztschr. f. Untersuch d. Lebensmitt.* 65:145, 1933.

208. Vilter, R. W., Vilter, S. P., and Spies, T. D. Relationship between nicotinic acid and a codehydrogenase (cozymase) in blood of pellagrins and normal persons. *J.A.M.A.* 112:420, 1939.

209. Vilter, R. W., Woolford, R. M., and Spies, T. D. Severe scurvy. A clinical and hematologic study. *J. Lab. & Clin. Med.* 31:609, 1946.

210. Waldenstrom, J. The incidence of iron deficiency (sideropenia) in some rural and urban populations. *Acta med. Scandinav.* (supp.) 170:252, 1946.

211. Walsh, G. E. K. Vitamin C levels in a P.O.W. camp. *Brit. Dent. J.* 79:208, 1945.

212. Williams, R. D., Mason, H. L., Power, M. H., and Wilder, R. M. Induced thiamine (vitamin B_1) deficiency in man. Relation of depletion of thiamine to development of biochemical defect and polyneuropathy. *Arch. Int. Med.* 71:38, 1943.

213. Williams, R. D., Mason, H. L., and Wilder, R. M. The minimum daily requirement of thiamine of man. *J. Nutrition* 25:71, 1943.

214. Wintrobe, M. M. Clinical Hematology. (Ed. 2) Philadelphia, Lea, 1946.

215. Wright, I., and Ludden, J. B. Treatment with vitamin C (cevitamic acid–ascorbic acid). *Med. Clin. North America* 24:743, 1940.

216. Yarbrough, M. E., and Dann, W. J. Dark adaptation and blood vitamin A measurements in a North Carolina nutrition survey. *J. Nutrition* 22:597, 1941.

217. Youmans, J. B., and Patton, E. W. The laboratory diagnosis of nutritional deficiencies. *Clinics* 1:303, 1942.

218. Youmans, J. B., Patton, E. D., Sutton, W. R., Kern, R., and Steinkamp, R. Survey of the nutrition of populations. *Am. J. Pub. Health* 33:955, 1943.

219. Youmans, J. B., Patton, E. W., Sutton, W. R., Kern, R., and Steinkamp, R. Survey of the nutrition of populations. *Am. J. Pub. Health* 34:368, 1944.

220. Youmans, J. B., Patton, E. W., Sutton, W. R., Kern, R., and Steinkamp, R. Survey of the nutrition of populations. *Am. J. Pub. Health* 34:1049, 1944.

221. Youmans, J. B., Patton, E. W., Sutton, W. R., Kern, R., and Steinkamp, R. Survey of the nutrition of populations. *Am. J. Hyg.* 42:254, 1945.

222. Yudkin, J. Nutritional deficiency in the pathogenesis of disease. *Brit. M. J.* 1:5, 1944.

Chapter 5

RADIOLOGIC EXAMINATION OF THE DIGESTIVE TRACT

Ross Golden

CERTAIN nutritional disorders are associated with or may cause abnormalities in the form and motor function of portions of the digestive tract, demonstrable by roentgen examination with barium sulphate preparations. The esophagus is rarely disturbed in these conditions. The small intestine is by far the commonest site of these abnormalities, with the stomach occasionally manifesting sluggish motor function. The large intestine has been described as hypotonic and hypomotile in sprue, but this seems to be of little clinical significance compared with the abnormalities of the small intestine.

ESOPHAGUS

PLUMMER-VINSON'S SYNDROME: SIDEROPENIC DYSPHAGIA

Plummer-Vinson's syndrome was originally described as a functional disorder of swallowing, with anemia and enlargement of the spleen, and was attributed to hysteria. Subsequent observations have shown that the dysphagia and anemia are associated with glossitis, cracking of the skin at the corners of the mouth, and other evidences of nutritional disorders. The difficulty in swallowing seems to occur in the upper end of the esophagus where webs or bands are found, usually in the postcricoid region. They appear as very narrow constrictions or as narrow, slitlike indentations in the barium shadow of the upper part of the esophagus as far down as the level of the aortic arch.[14] This condition is now called "sideropenic dysphagia." Opinions have been expressed that this condition predisposes to carcinoma of the esophagus. It seems that a nutritional deficiency is associated with the dysphagia and that the nutritional disorder may be a primary, rather than a secondary factor as originally supposed.

STOMACH

In association with some nutritional disorders the motor function of the stomach is abnormal, as demonstrated by x-ray examination with barium sulphate preparations. Six-hour barium residues are found which must be explained on the basis of ineffective peristalsis, inasmuch as no pyloric obstruction can be demonstrated. This delay in the emptying of the stomach disappears with proper treatment of the nutritional disorder.

Atrophy of the mucous membrane has been described by gastroscopists in patients with pernicious anemia. Treatment with liver extract is associated in some cases with a return to the normal appearance of the mucous membrane.

SMALL INTESTINE

The most important effect of nutritional disorders is manifested in the small intestine as abnormalities of form and motor function, demonstrable by x-ray examination. Some of these abnormalities occur in conditions in which vitamin deficiency plays either a major or a minor role. They seem to be associated with edema of the intestinal wall, whatever may be its cause.

Attention was called to these intestinal abnormalities by Mackie[8] in a case of sprue, and by Snell and Camp[13] in "chronic steatorrhea." Since then they have been described by other writers in a variety of conditions, e.g., in ulcerative colitis by Mackie, Miller, and Rhoads,[9] in celiac disease by a number of writers[1, 2]

TECHNIC OF EXAMINATION

Abnormalities of the small intestine are sometimes noted in connection with a routine barium examination of the stomach and duodenum, or of the large intestine with a barium enema. They are best demonstrated by the small intestine study which is described in detail by Golden.[3] The patient, after fasting overnight, is given 4 oz. of pure barium sulphate in distilled water or, as preferred by Golden, in normal saline. A series of films of the entire abdomen is then taken at half-hourly intervals for four to five hours. The films are developed and inspected soon after they are taken. Fluoroscopic examinations are made two or three times during the procedure as indicated.

Schatzki[12] prefers to pass a small tube through the stomach and duodenum into the jejunum, through which the entire small intestine can be filled with fluid barium suspension; this is called the "small intestinal enema."

The Normal Intestine

The x-ray examination of the small intestine gives information regarding (1) motility, i.e., the movement of the opaque material, (2) the width or caliber of the lumen, and (3) the relief contours of the inner surface. The interpretation of the examination must be based on a knowledge of the anatomy and physiology of the normal small intestine (Fig. 6) which cannot be reviewed in detail here.[3] Barium in a saline suspension reaches the cecum in from one and one-half to three hours after ingestion. The width of the jejunal shadow averages from 2.5 to 3.0 cm. and that of the ileum 2.0 to 2.5 cm. The caliber is usually fairly even except where contractions occur. Normal contractions are relatively short, 2 to 4 cm. in length. As a peristaltic movement flows along, the walls behind it should promptly relax. The mucosal folds of the normal adult jejunum are high and lie close together, giving its barium shadow the characteristic feathery appearance. In the lower segments of the small intestine, the mucosal folds are lower and farther apart. In the lower ileum they may not be visible except on films taken with the ileum under pressure.

The intestine of the normal young infant is quite different in appearance from that of the normal adult. The transit time of the barium through the infant's intestine is slow by adult standards. The jejunum at first shows no or very few and very low mucosal folds. The caliber of the lumen is very uneven and marked segmentation is present. The age at which the normal young child's intestine acquires the appearance of that of the adult varies greatly in different individuals.[15]

Nutritional Disorders

Disorders of nutrition may be divided roughly into two broad groups:

1. Primary nutritional disorders, which develop without an obvious anatomic cause, for example, celiac disease and sprue.
2. Secondary nutritional disorders, in which the condition is caused

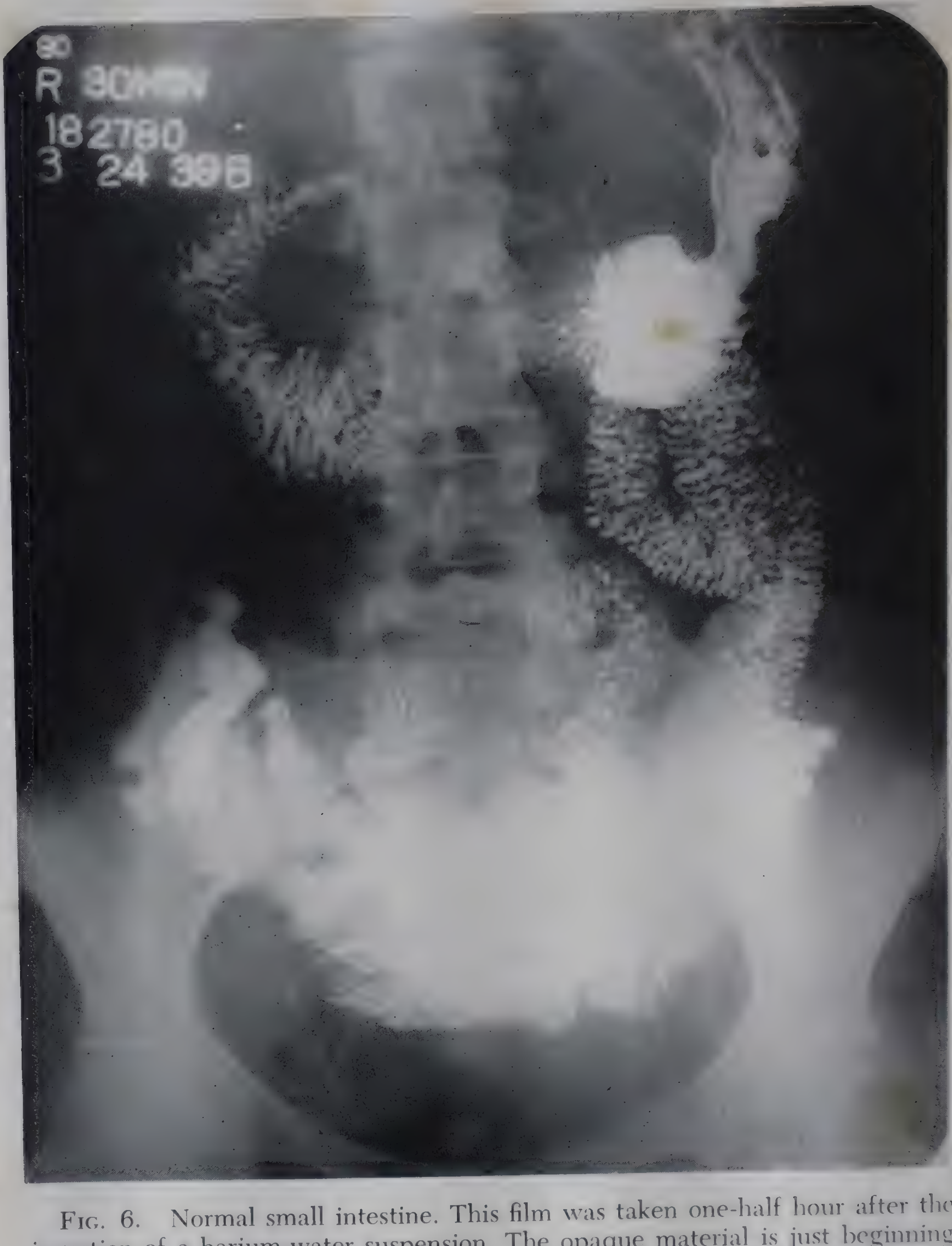

Fig. 6. Normal small intestine. This film was taken one-half hour after the ingestion of a barium-water suspension. The opaque material is just beginning to enter the cecum, a transit time which is shorter than the average. The pattern of the loops is normal. The width of the shadow is even except in two or three places where it is narrowed by peristaltic constrictions. The jejunum is a little wider than the ileum. The mucosal folds of the jejunum are normally high, closely and evenly spaced, and regular in width. The mucosal folds of the ileum are fewer in number, farther apart, and lower in height than those of the jejunum. The position in the abdomen of the various portions of the small intestine is as usual except that more loops are often present in the right flank.

by, or is at least associated with, diseases which may interefere with the ingestion, digestion, or absorption of nutriment, such as carcinoma of the stomach, peptic ulcer, organic disease of the small intestine or mesentery.

The clinical manifestations of nutritional disorders are variable and their significance is often obscure. Symptoms of a disturbance in the digestive tract which often lead to a roentgen examination are likely to be present, and thus an opportunity is afforded to demonstrate the disordered motor phenomena discussed below.

Nutritional disorders may occur at any age, from the newborn to the aged. Those which affect the small intestine are usually associated with other evidences of abnormal intestinal physiology such as a flat blood-sugar curve after the ingestion of glucose. This occurs with minor disorders[7] as well as in severe, advanced conditions such as sprue.

The roentgen manifestations in the small intestine vary with the severity and duration of the disorder and with other factors which are not understood. The most important are:

1. Disordered motor function:

A. *Hypomotility:* In the more advanced stages the barium may not reach the cecum in six hours or longer.

B. *Hypotonicity:* In the more advanced stages, the lumen of the intestine may vary from normal to more than twice normal width.

C. *Hypermotility* and *hypertonicity:* In the earlier stages, and in some of the more advanced cases after beginning treatment, the jejunum may be narrower than normal and may pass the barium along very rapidly.

D. *Abnormal segmentation:* Areas of more or less persistent narrowing, of different and varying lengths, divide the barium shadow into segments. Frequently the narrowing is sufficient to expel all of the barium from the contracted area, which gives the appearance of discrete masses of barium in the distended areas. This is called "clumping of the barium" by some writers (Fig. 7A) and is a manifestation of the inability of the intestine to relax. It is probably best explained as a disorder of the intramural reflex mechanism which coordinates and controls the propulsive movements of the intestine. In the advanced stages of nutritional disorders, e.g., in sprue, the filled segments are usually wider than the normal lumen and are usually associated with hypomotility. In the earlier stages, the masses of barium are shorter and may be the width of the normal lumen or narrower. The masses of opaque material, whether large or small, are usually fusiform in shape but may be well rounded. Segmentation is usually more pronounced in the middle third of the intestine; in the less advanced stages and in patients responding to treatment, it may be present only in this region. Fluoroscopic examination in the advanced cases reveals very little movement of the intestine, and

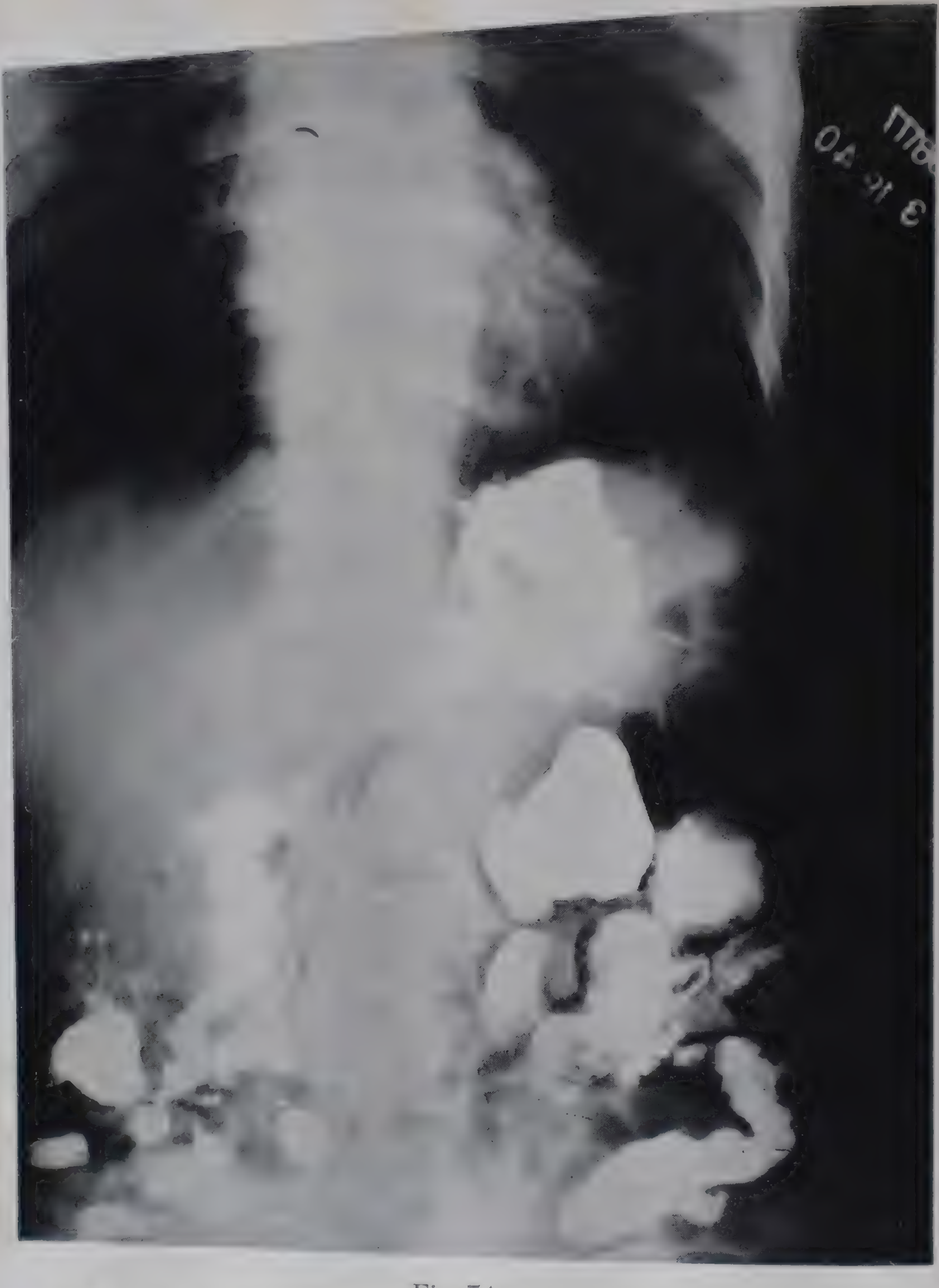

Fig. 7A

Fig. 7. Nutritional disorder with anemia. *A*. Examination of the intestine March 18, 1940 shows loops of jejunum filled with barium. In 6 hours the opaque material did not reach the cecum. The jejunum is dilated and abnormally segmented. Its mucosal folds are not visible. (For clinical summary see caption to Figure 7*B*.)

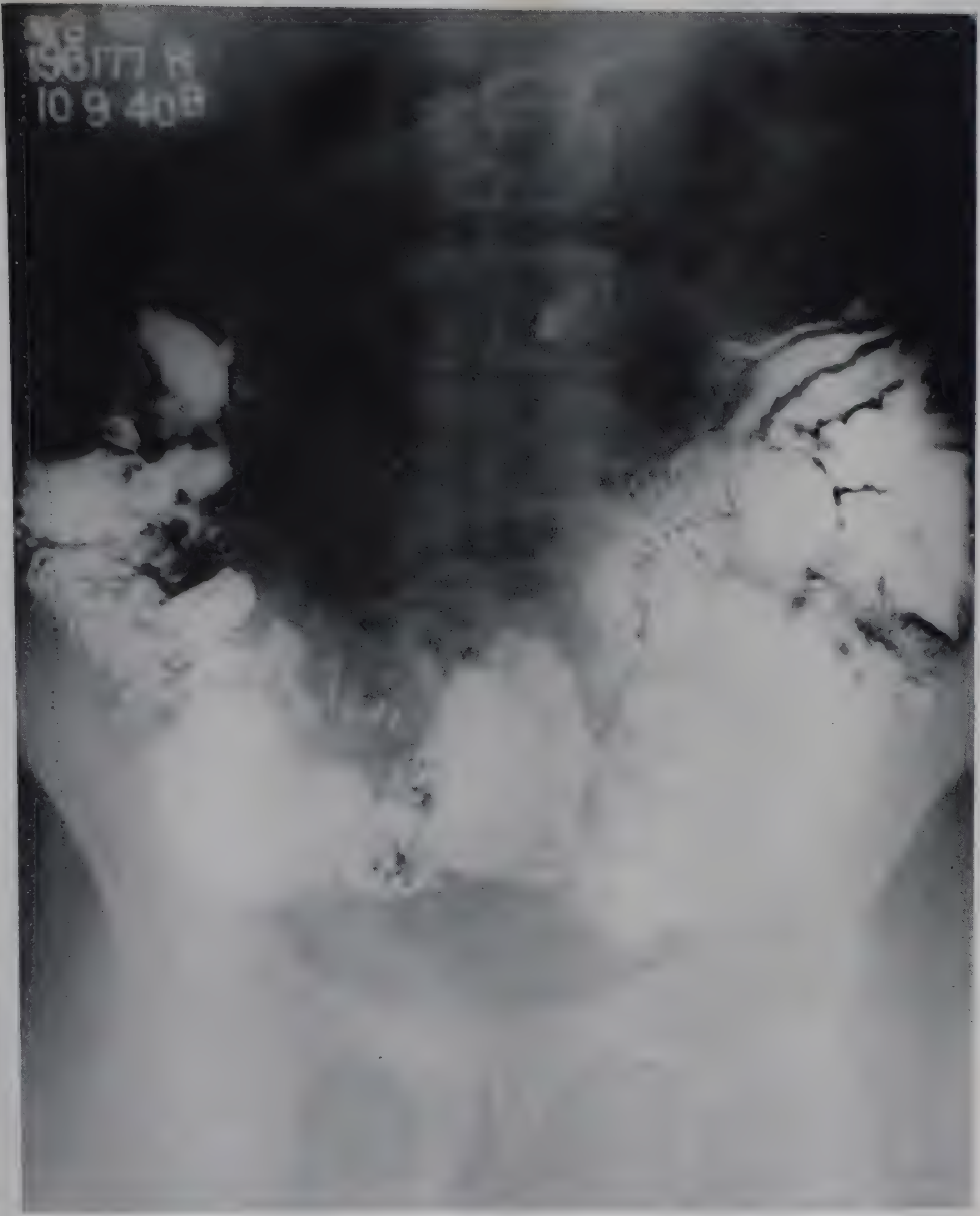

FIG. 7 (*continued*). *B*. Examination of the intestine October 9, 1940, after six months of treatment, with great clinical improvement, shows no segmentation. Mucosal folds can be seen but they are not entirely normal in width, height and spacing. The motor function of the small intestine is greatly improved but is still not normal.

A man, 61, (Unit No. 603286) was admitted to the hospital because of a loss of 20 lb. in weight during the previous six months, loss of strength and appetite, and nausea and vomiting for two months. He had severe hyperchromic anemia, leukopenia, and an elevated erythrocyte sedimentation rate. No free HCl was present in the gastric juice. The blood protein was normal. He improved rapidly with intramuscular injections of concentrated liver extract.

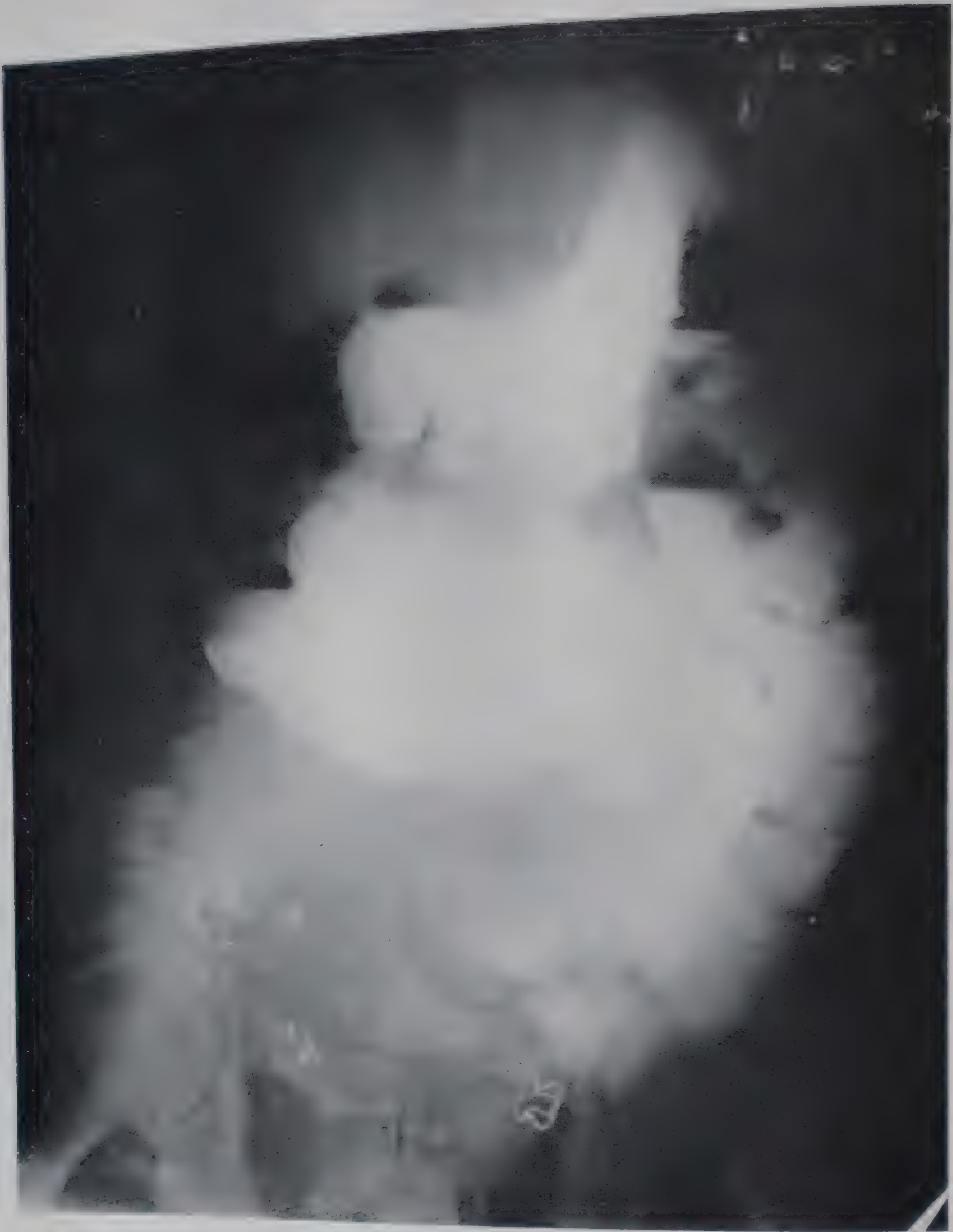

FIG. 8. Sprue. This film was taken in the erect position six hours after the ingestion of a commercial barium preparation and after the stomach was filled again. In six hours the opaque material had not reached the cecum. The jejunum is dilated and contains considerable gas. Fluid levels can be seen. The margins of the jejunum appear smooth because the mucosal folds have been obliterated.

A man, 34, (Unit No. 473118) was admitted December 5, 1935, because of a loss of 25 lb. during the previous four months, and diarrhea of two months' duration. He had intermittent attacks of chills and fever, and of epigastric propulsive contractions when they do occur appear sluggish in contrast to those of the normal intestine.

The muscle coat of the intestine is stimulated by the parasympathetic division of the autonomic nervous system and is inhibited and relaxed by the sympathetics. It has been shown that nerve stimulation affects muscle, glands, etc. through the production of diffusible substances at the end plates (the chemical mediator theory of nerve action). The parasympathetics produce acetylcholine. The sympathetics produce epinephrin (adrenalin) or something physiologically indistinguishable from it. Structures stimulated by the parasympathetics are referred to as "cholinergic" and those stimulated by the sympathetics as "adreninergic." The muscle coat of the intestine is a cholinergic structure.

2. Changes in the mucous membrane. The mucosal folds of the normal small intestine are produced and are changed by action of the muscularis mucosae which is independent of that of the muscle coat. The muscularis mucosae is supposed to be adreninergic and therefore stimulated by the sympathetic division of the autonomic nervous system.

A. *Obliteration or a reduction in the number of the folds* (Fig. 8): In well-advanced nutritional disorders, for example in sprue, the intestine has an abnormally smooth appearance as the result of obliteration or reduction in the number of the mucosal folds. This is best seen in the jejunum where these folds are normally high and lie close together.

B. *Exaggeration of the folds:* In many cases, instead of being obliterated the folds are abnormally wide and are irregular in width, height, and spacing.

C. *Gas and fluid levels:* Gas may be present in considerable amounts. This has been interpreted as evidence of the inability of the mucosa to absorb gas entering it from the stomach. In advanced stages, films taken with horizontal rays show gas and fluid levels (Fig. 8). This may, at first glance, be considered suggestive of ileus.

Exaggeration or obliteration of the mucosal folds may be taken as evidence of a disturbance in the function of the muscularis mucosae. Flat blood-sugar curves after the ingestion of glucose, as found in sprue, in

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distress relieved by induced vomiting. The stools were light and foamy, and contained fatty acid crystals. The abdomen was enlarged. The tongue was red and dry. Two injections of liver extract and a "sprue diet" including bananas were followed by prompt improvement. One year later, roentgen examination showed that coarse mucosal folds had reappeared in the jejunum, but hypomotility and segmentation persisted. In 1940 he recalled that, as a child 2-3 years old, he had severe diarrhea and almost died. Roentgen examination May 1, 1940 showed no abnormality of the small intestine except a slow transit time.

celiac disease of young children, and in some of the milder nutritional disorders[7] are further evidence of abnormal mucosal physiology.

It is of interest that the pattern of the small intestine of the normal infant is very similar in appearance to that of the adult with well-developed sprue.

The above-described phenomena may be conveniently called "disorder of the motor function" of the small intestine.

The mechanism whereby this disordered motor function of the small intestine is produced is not clear. Inasmuch as proper function of the intramural nervous system is necessary to coordinate and regulate intestinal movement, a reasonable hypothetical explanation for it could be a disturbance in the function of these nerves. Some observations have been published which support this hypothesis. May and McCreary[10] and May, McCreary, and Blackfan[11] found that the injection of mecholyl (a stable form of acetylcholine, the substance produced by the parasympathetic nervous system) in children with celiac disease improved both the intestinal movements and the absorption of glucose. Ingelfinger and Moss[4] showed by means of a balloon in the intestine of patients with sprue, (1) that the tonus was low and that movements were very sluggish, (2) that the injection of prostigmine, which inhibits the destruction of acetylcholine by the enzyme cholesterinase, had little or no stimulating effect, and (3) that the injection of mecholyl (acetylcholine) was immediately followed by active movements of the intestine. Ingelfinger and Moss concluded that in sprue the intramural nervous apparatus is unable to liberate active acetylcholine. In a case of well-advanced sprue under treatment, I confirmed the observations of these authors by fluoroscopy of the intestine after the injection of a barium suspension through a tube in the jejunum.

A 38-year-old woman (Unit No. 777325) was admitted January 14, 1948, complaining of gas pains and indigestion of about thirteen years' duration. Appendicectomy, followed by acute mechanical ileus, was done six years previously. At that time the record contains a comment on her malnutrition. She came to the clinic in December, 1937, because of belching, epigastric fulness, and a red beefy tongue. The blood sugar curve after the ingestion of glucose was flattened (Fasting, 78; ½ hr., 117; 1 hr., 68; 2 hr., 83; 3 hr., 87). A small intestine study January 8, 1941, two films of which are shown, disclosed slow emptying of the stomach, marked segmentation in the middle third of the intestine, delayed but marked coarsening of the mucosal folds of the jejunum, and a nine-hour residue of barium in the ileum. She was given a potent whole vitamin B preparation by mouth. The symptoms were relieved and she gained weight. On March 19, 1941, the blood sugar curve after the ingestion of glucose was essentially normal (Fasting, 90; ½ hr., 133; 1 hr., 79; 2 hr., 81). A small intestine study March 27, 1941 (Fig. 9C) disclosed an essentially normal small intestine pattern.

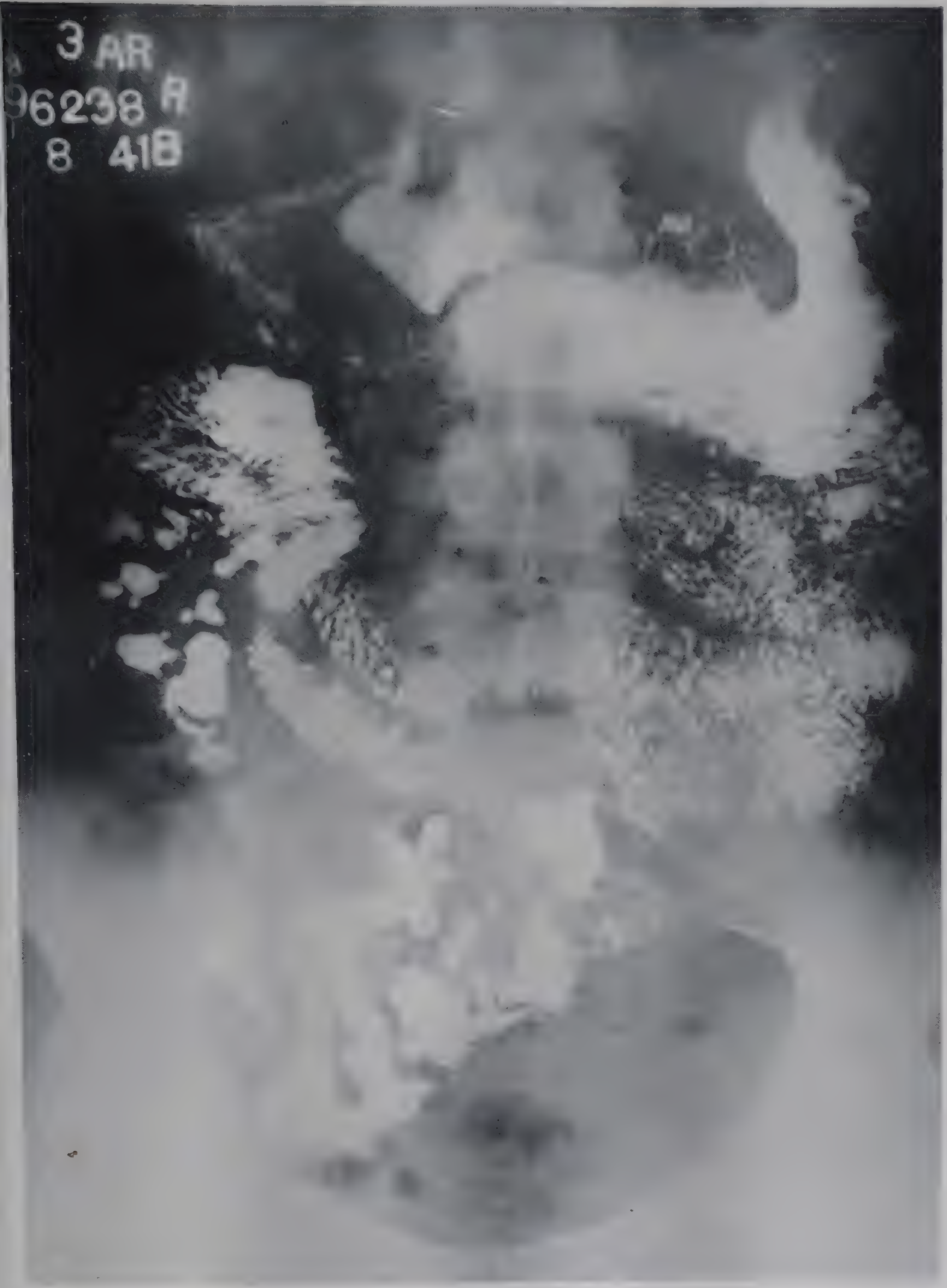

Fig. 9A

Fig. 9. Mild nutritional disorder. *A.* Films made at 3 hours during a small intestine study show that the stomach was emptying slowly. Transit time in the small intestine was slower than average. Marked abnormal segmentation was present in the upper ileum. (For clinical summary see note on opposite page.)

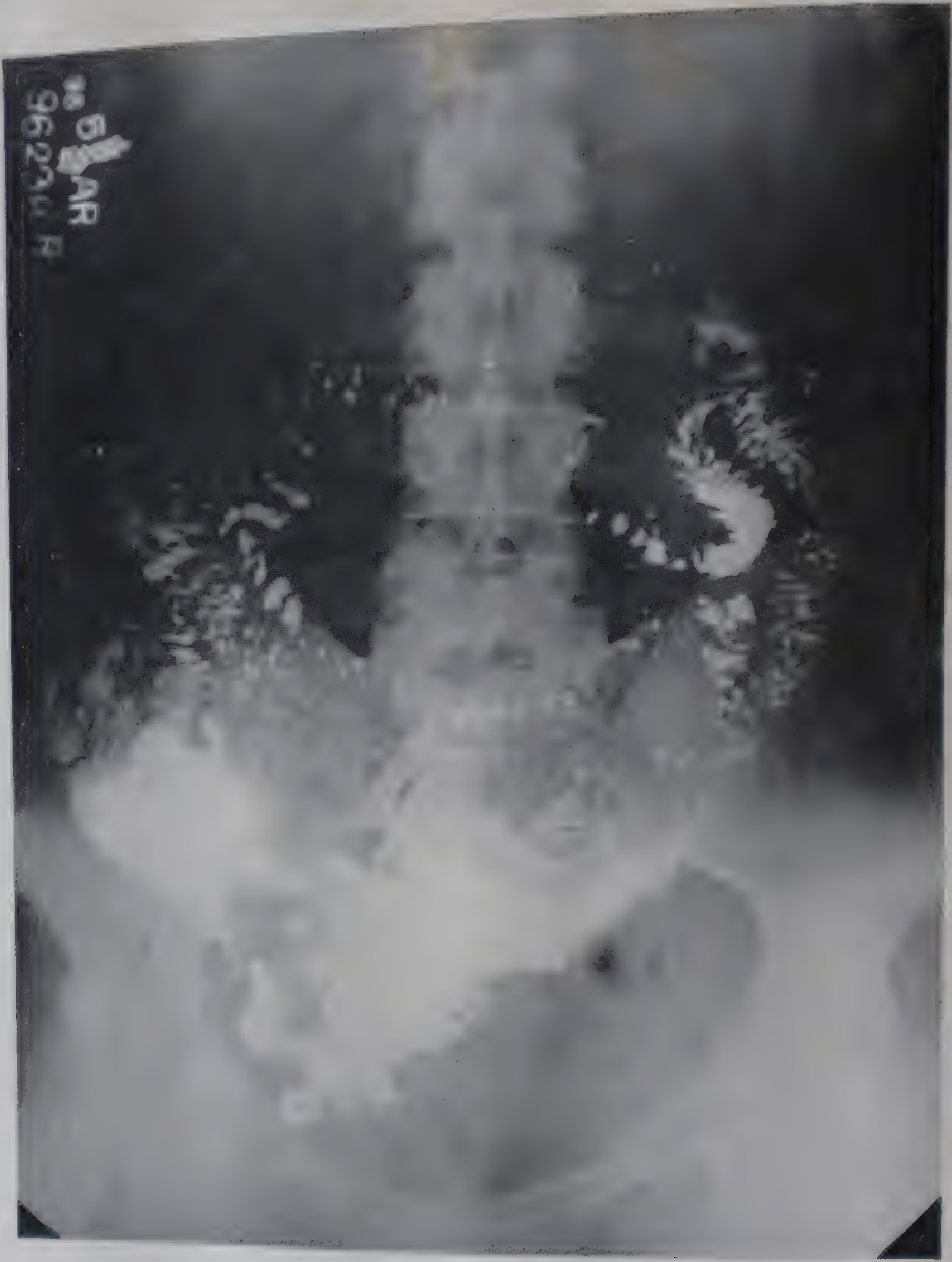

Fig. 9B

Fig. 9 (*continued*). *B*. At 5 hours the stomach was empty. The mucosal pattern of the jejunum became very coarse. The segmentation in the ileum was not as marked as at three hours. Barium had reached the cecum. (For clinical summary see note, p. 166.)

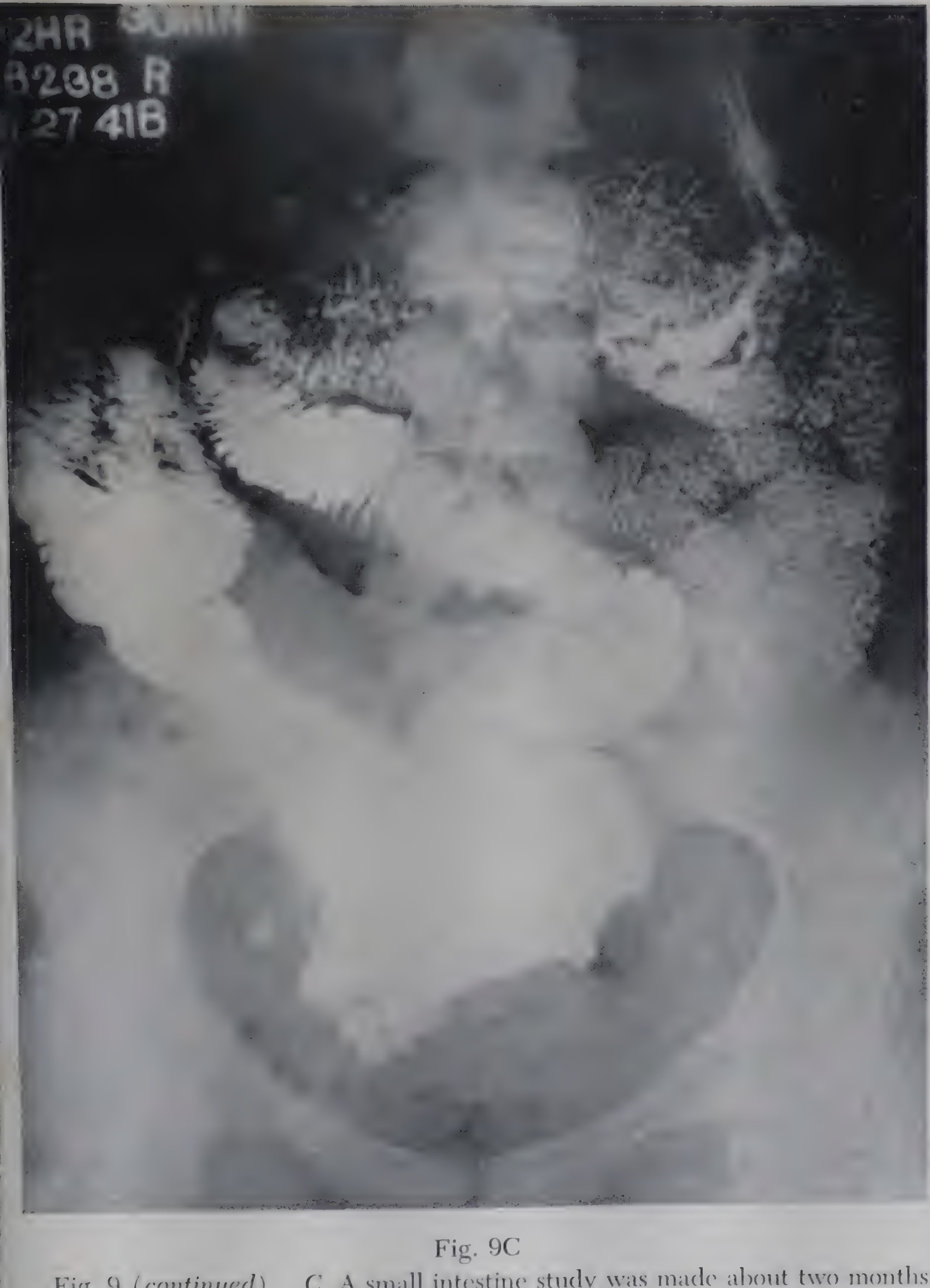

Fig. 9C

Fig. 9 (*continued*). C. A small intestine study was made about two months after beginning treatment with the whole vitamin B complex. This film at 2½ hours shows evidence of normal emptying of the stomach. The head of the barium column was in the lower ileum at 2½ hours. Abnormal segmentation was no longer present. The caliber of the lumen and the mucosal pattern were normal. (For clinical summary see note, p. 166.)

EFFECT OF TREATMENT

Except in the most advanced, severe nutritional disorders, appropriate treatment is followed by improvement in the motor function of the intestine. Mucosal folds reappear (Fig. 7B) or, if exaggerated, become normally narrow and evenly spaced. Slow transit time may be temporarily replaced by abnormally rapid movement, and then motility becomes normal. The objective improvement disclosed on repeated roentgen examination usually lags behind improvement in the patient's clinical condition.

The nutritional disorder may reach a stage in which it fails to respond to treatment including the parenteral administration of liver extract. The disease is then described as irreversible.

NONSPECIFICITY OF DISORDERED MOTOR FUNCTION

The abnormalities of the small intestine discussed above were first demonstrated in patients with steatorrhea.[8, 13] Subsequent observation has shown that disordered motor function occurs in many conditions other than the recognized clinical entities such as sprue and pellagra.

Disorders of nutrition may be superimposed upon almost any disease of the gastrointestinal tract. The symptoms may be precipitated by operation, by diarrheal states (as in chronic colitis or amebiasis), by therapeutic restriction of diet, (as for duodenal ulcer), etc. Nutritional disorders have been observed with pancreatic lithiasis, with carcinoma of the pancreas, with regional enteritis.

Disordered motor function of the intestine has been observed in association with chronic sclerosing mesenteritis, with diseases of the liver and biliary tract, with extensive infiltrating neoplasms of the small intestine, and with hypoproteinemia.

Lepore and Golden[7] described a syndrome in a group of patients, mostly young adults, which consisted of abdominal pain, a flat oral-dextrose-tolerance curve, increased capillary fragility, and disorder of the motor function demonstrated on roentgen examination of the small intestine. Some of these patients were plump or even slightly obese, but many showed evidence of a poorly balanced diet. The signs and symptoms in these cases were improved following the administration of the whole vitamin B complex and of liver extract (Fig. 9).

PATHOLOGY

The pathology of the small intestine in nutritional disorders has not been very well studied. It has been reviewed elsewhere[3] and cannot be recapitulated here.

One pathologic finding, which is common to a number of the conditions associated with disorder of intestinal motor function, is widening of the submucosa with edema and round cell infiltration, or with edema alone. Edema fluid collects largely in the loose submucosa; this is responsible for the widening of the mucosal folds, usually taken as evidence of edema of the mucosa itself. It seems probable that this edema plays a part in the disturbance of intestinal movements but it is not clear how this is effected.

HYPOPROTEINEMIA

A common cause of edema is hypoproteinemia. The osmotic pressure of the blood depends in large part upon the albumen fraction of the serum protein. It has been shown that the "edema level" of serum protein is approximately 5.5. The NaCl concentration also plays a part in the transfer of fluid from the blood vessels to the tissues. Edema develops quickly when an excess of normal saline solution is given parenterally in the presence of a low serum protein. This may be responsible for the development of paralytic ileus as complication of a mechanical ileus. A man with severe burns over the upper part of the body developed acute paralytic ileus as the result of hypoproteinemia produced by the exudation of serum from the burned areas and the dilution of the blood by intravenous saline infusions; when the infusions were stopped and plasma was given, the ileus disappeared as the blood protein increased to normal levels. Jones and Eaton[5] pointed out the deleterious effect on gastrointestinal activity of low blood protein and of excess intravenous saline infusions after operation in patients with gastrointestinal disease. They found that under these circumstances edema of the lungs could develop in the absence of peripheral edema as the result of hypoproteinemia. Lepore[6] showed in dogs that edema fluid collected in the submucosa of the intestine before it could be demonstrated elsewhere.

The demonstration of disordered motor function of the small intestine in a patient with gastrointestinal disease should suggest the possibility of low blood protein, and the advisability of determining the blood protein level and correcting it before an operation is performed if hypoproteinemia is found.

CONCLUSION

The demonstration of disordered motor function of the small intestine, in view of its nonspecificity, cannot be taken as pathognomonic of any particular disease or dysfunction. However, recognition of these disturbances of the small intestine may serve to call attention to certain possibilities, including nutritional disorders. In view of the obscure symptoms in early cases, these observations are important, because timely treatment may prevent the development of the more advanced stages and the complications of nutritional deficiencies.

BIBLIOGRAPHY

1. Fanconi, G. Der intestinale Infantilismus und ähnliche Formen der chronischen Verdauungstörung. *Abh. Kinderh. H.* 21:1, 1928.
2. Golden, R. The small intestine and diarrhea. *Am. J. Roentgenol.* 36:892, 1936.
3. Golden, R. The Radiologic Examination of the Small Intestine. Philadelphia, Lippincott, 1945.
4. Ingelfinger, F. J., and Moss, R. E. The motility of the small intestine in sprue. *J. Clin. Investigation* 22:345, 1943.
5. Jones, C. M., and Eaton, F. B. Postoperative nutritional edema. *Arch. Surg.* 27:159, 1933.
6. Lepore, M. J. Experimental edema produced by plasma protein depletion. *Arch. Int. Med.* 50:488, 1932.
7. Lepore, M. J., and Golden, R. A syndrome due to deficiency of the vitamin B complex. *J.A.M.A.* 117:918, 1941.
8. Mackie, T. T. Non-tropical sprue. *M. Clin. North America* 17:165, 1933.
9. Mackie, T. T., Miller, D. K., and Rhoads, C. P. Sprue: roentgenologic changes in the small intestine. *Am. J. Trop. Med.* 15:571, 1935.
10. May, C. D., and McCreary, J. F. The glucose tolerance test in celiac disease, significance of low blood sugar curves. *J. Pediat.* 17:143, 1940.
11. May, C. D., McCreary, J. F., and Blackfan, K. D. Notes concerning the cause and treatment of celiac disease. *J. Pediat.* 21:289, 1942.
12. Schatzki, R. Small intestinal enema. *Am. J. Roentgenol.* 50:743. 1943.
13. Snell, A. M., and Camp, J. D. Chronic idiopathic steatorrhea: roentgenologic observations. *Arch. Int. Med.* 53:615, 1934.
14. Waldenström, J., and Kjellberg, S. R. The roentgenological diagnosis of sideropenic dysphagia (Plummer-Vinson's Syndrome). *Acta Radiol.* 20:618, 1939.
15. Zwerling, H., and Nelson, W. E. The roentgenologic pattern of the small intestine in infants and children. *Radiology* 40:277, 1943.

Chapter 6

CRITIQUE OF LABORATORY AIDS IN THE DIAGNOSIS OF MALNUTRITION

Herbert Pollack

THE lack of truly adequate methods of determining nutritive status of individuals will delay the full clinical application of the information developed in the research laboratories. The clinician is in need of rapid, accurate, economical, and practical methods of assay. The presumptive diagnosis of nutritional inadequacy can be made by the clinical examination of the patient. This diagnosis should then be confirmed by therapeutic trial or laboratory examination of the tissues, blood, urine, or feces. Therapeutic trial is not without its drawbacks. Though many morphologic lesions, especially those that are acute, respond rapidly to adequate therapy, a long time is usually required for the reversal of chronic morphologic changes. Many of the deficiency phenomena may have been present long enough to be irreversible.

In the development of the field of nutrition, a concerted effort is therefore being made to develop such laboratory aids for the diagnosis of nutritional disturbances. It is only natural that the use of chemical methods be explored. After the technical problem of the actual analysis has been solved, there remains the very important one of interpreting the figures. The clinician is interested in interpreting chemical findings with respect to any one individual patient. The public health officer is interested in a group as a whole under his observation. It can be said that the present development of the chemical technics is more applicable to group studies than to individuals. The group survey technic gives data as to the immediate preceding nutritive intake of a cross section of people. Individual variations are minimized by the statistical analysis of the figures. One is enabled to compare the current nutritive intake of one group with another; or even the same group at different times of the year. All this material is important data for the further understanding of the nutrition of the population. These methods, however, give little help to the clinician who wants to prove or disprove that a given observed lesion is the result of a previous malnutrition in a given individual (see Chapter 4).

Nutritional disturbances adversely affect every tissue of the body. The effect may vary in degree and in kind with the individual tissue. The specific nutrient deficiency may determine the tissue changes. The individual tissue characteristics will modify this change.

These tissue effects may be reflected in morphologic changes, functional changes, and in alterations of the chemically analyzable constituents. The morphologic changes have a time factor for their development. Procedures must be evolved to measure the functional changes and determine their early deviations. These would be the simplest ways of measuring nutritional disturbances, but not the most reliable because of the nonspecific* nature of their changes. The more important ones may be enumerated briefly as: (1) basal metabolic rate, (2) heart action, (3) temperature regulation, (4) reflex arc changes, (5) physical performance of work, and (6) the possible interrelationship of these to one another.

Analytic procedures must be developed to show the changes in concentrations of the nutrients, their functional components or degradation products. The limitations of direct tissue analysis for these are quite obvious. If, as is frequently stated, tissue concentrations are in equilibrium with the circulating blood, a method should be available to study tissue changes indirectly. Attempts to solve the problem this way have not been entirely satisfactory. The quantities of many of the nutrients have been too small to measure accurately. The methods of analysis are complex and too time-consuming for simple clinical application.

It was then argued that the concentration of the urinary constituents reflected to a certain extent the metabolic activities of the tissues. This was a possible approach of the problem. It became apparent as the studies proceeded, however, that the urine concentration of metabolites and nutrients was dependent upon a great many factors. To a very large extent they reflected only the immediate preceding nutrient intake.

The questions that had to be answered had other complicating features. As soon as one starts to study means of appraisal of nutritional states, one is impressed with the extent of the metabolic adaptations to malnutrition, emaciation, and starvation. The rate of development of the malnutrition seemed to determine the end results, for there are adaptation mechanisms in slowly developing malnutrition which are not found in rapidly developing malnutrition.

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* This point of non-specificity has been discussed in Chapter 3, p. 53. (*Editors.*)

With these various factors becoming apparent, it was difficult to determine what tests and measurements would consistently give the most reliable information as to the state of nutrition. In addition to knowing the state of nutrition, one must know when the changes are critical enough to become a hazard to health and/or interfere with the economic usefulness of the individual to his community and to himself.

A study of the literature in the general field of vitamin tissue concentrations leads to the conclusion that our present state of knowledge is fragmentary and inexact. Many speculate on the fundamental roles of the various tissues and organs. It is usually assumed that a knowledge of the distribution of the vitamins in the various tissues will ultimately help in determining the functions of these vitamins. This assumption must be taken with a good deal of skepticism. For example: vitamin A is extremely important in vision. In the dog the vitamin A content of the eye may only be 0.001 per cent of the total amount in the animal. The vitamin C content of the adrenal glands is out of proportion to that of the rest of the body. Does that mean that there is storage of vitamin C in the adrenals, or can it be interpreted to mean that vitamin C is important in the functioning of that gland? Certainly the known facts about the effects of the deficiency of vitamin C, with respect to the formation of intercellular material in bone and other tissue, give no indication as to the mechanism of its action. The distribution of this vitamin, as well as vitamin A, in the tissues gives no lead as to their functions.

Even after the analytic problems are solved, many problems arise in the interpretation of the results. Nicotinic acid can be cited as a good example. In the urine one finds nicotinic acid, N^1-methylnicotinamide, trigonelline, and nicotinuric acid. Of these only N^1-methylnicotinamide has been shown to reflect with any degree of probability the metabolic activity of this vitamin. Strangely enough the nicotinic acid in the urine does not fluctuate to any extent with the metabolic activity. If this is true for one vitamin, when will we find the metabolic products of the other vitamins? There is some indication that thiamine and pyrimidine are related in the same manner. Riboflavin in the blood presents another problem. Free and conjugated forms are found. Which is the most significant? Is the riboflavin in the red blood cell more important as a nutritive index than that in the white blood cell? Or are these merely constants, and the plasma level the most important metabolic index?

The method of analysis also influences the results considerably. The microbiologic technics do not always give results comparable to the chemical determinations in the same material. These two, in turn, vary considerably from the animal assay methods. Microbiologic assay methods usually do not require extractions or isolation of the substance to be analyzed. On the other hand, other substances closely related may give the same growth stimulus. The question arises as to whether, in the extractions required for chemical analysis, there is some loss of the substance from incomplete extraction and/or alterations in the chemical structure because of the treatment.

These aspects of the analytic procedures may account in part for the wide divergence of reports in the literature.

Theoretically the first changes that occur during the restricted nutritional intakes are biochemical. These should be measurable before functional or morphologic changes can be detected. On any planned regimen where the dietary intake is known and controlled, it is a very simple matter to correlate intake, blood concentrations, and urinary excretions. The very simplicity of this relationship has been a stumbling block in the approach to the clinical interpretation of urinary excretion estimations. It must be emphasized, too, that the reverse of this situation holds just as true. In a depleted individual, showing clinical, functional, and morphologic signs of deficiency states, the administration of the vitamins, or other specific nutrients, leads to an immediate increase in the excretion levels long before there are functional or morphologic changes. It becomes apparent, therefore, that the simple assay of the urine gives no indication beyond the immediate past of the individual. Any correlation of random urine excretion levels with clinical observations is then impossible. These facts have been well recognized and applied for a long time with respect to nitrogen excretion in the urine. It is universally accepted that one cannot appraise the protein status of a patient by simply determining the amount of nitrogen in the urine. A patient may be in nitrogen balance at almost any level of excretion. It is also true that a patient may be in negative, positive, or perfect balance at exactly the same levels of urinary nitrogen excretion. High nitrogen excretion can be the result of high intakes or high catabolic rates of protein metabolism. In the first case, the patient may be in positive nitrogen retention or nitrogen balance. In the second he could be in a negative nitrogen balance. It is virtually impossible to judge the current nutritional status from a simple study of concentration of nutrients or metabolic end products in the urine.

The urinary excretion levels have been found to reflect largely the immediately preceding nutrient intake. In addition, the influence of metabolic alterations in general have been found to influence vitamin excretion levels. A good example is the fluctuating relation of riboflavin excretions to the nitrogen balance of the patient. In a negative nitrogen balance riboflavin excretion may be high in the presence of a poor intake.

Attempts to circumvent these difficulties led to the development of the load tests, which have been applied to all the vitamins. These have been used and abused, but there is evidence that they may be a more reliable index of tissue storage than of simple urine excretion. For a load test to be of real significance, a physiologic amount of the vitamin should be administered subcutaneously or intramuscularly. The parenteral route insures rapid absorption. For the test to be clinically applicable, it must be of a short enough duration to be performed as an ambulatory procedure. It must be long enough to insure an accurate urine collection and produce sufficient excretion to be measurable. Four hours has been found to be quite satisfactory for both purposes.

The first laboratory instrument available to study nutrition was the scales. It is still of paramount importance in evaluating nutritional states. The rapid expansion of the knowledge of vitamins in recent years has distracted the attention from the basic requirements for growth and good health: adequate calories. Vitamins are only adjuvants helpful in enabling the body to utilize the calories. All the vitamins in the world would lead to starvation in the presence of inadequate caloric intake. Weight loss, or in the case of the child, failure to gain weight at the normal rate, are prime evidences of inadequate caloric utilization. In mass survey technics one can simply weigh a statistically significant number of people. These weights are categorized by sex and age. It is not even necessary to measure the height of adults for this technic, for it is assumed that if the number is great enough, the heights will average. The application of the criterion of weight to any one individual, however, is more complicated. The tables of reference are based upon sex, age, and height. There are two sets of tables available. The older figures are based upon averages of many thousands of individual weights. These weights are sometimes called "ideal." It must be emphasized that they are "average." "Ideal" weights have never been satisfactorily determined. The life insurance companies have recently made an attempt to determine this figure, based upon longevity. These newer weight data are somewhat lower for most age groups than the "averages" of old tables. The increasing weight of the adult in the older tables was a reflection of the decreasing metabolism of age and the constant level of intake. Weight of individuals should be studied serially. When the weight is determined, the state of hydration of the individual should be estimated.

Water, while not ordinarily considered a nutrient, is a most important item of the diet and body constituents. The percentage of water varies considerably with the age of the individual. A fetus, for instance, is about

90 per cent water; an adult about 72 per cent. Not only does the total amount of water vary, but also its distribution in the body. The intracellular water in the adult who is fully developed muscularly, comprises about 41 per cent. The infant's intracellular water is only about 31 per cent. The weight of the water, then, obviously influences very greatly the weight of the individual. Since the tissue water fluctuates most rapidly, it is frequently responsible for large shifts in body weight. There are methods available for determining this water partition in the body. The plasma volume can be determined by the dye method: a known amount of a nonpermeable dye is introduced into the blood stream, and after allowing sufficient time for even distribution a sample of blood is taken and the dye concentration determined. The hematocrit value is simultaneously estimated. This gives the plasma volume and blood cell volume. The extracellular fluid is determined by the thiocyanate method. The specific gravity of the body can be determined by immersion in water—this gives the fat content of the body. The tissue water is determined and variations give the index of the state of hydration.

The adequacy of the protein intake is best determined by a study of the nitrogen balance. That is, the amount of the nitrogen in the urine and feces must be equal to the amount of nitrogen ingested by the individual. It is a common belief that the serum protein concentrations reflect the adequacy of the nitrogen intake. This is true only in its broadest sense. One must not forget there is a time lag between deficient protein intake and the actual decrease in serum concentration. There are available large amounts of protein in the body which are depleted before any actual measurable change occurs in the circulating blood proteins. If the clinician is interested in early deficiency states before any measurable damage has been done, he cannot rely on the serum protein concentration as an index. When the circulating blood proteins drop below 6.0 Gm. in each 100 cc. of blood, it can be concluded that a severe, long-standing protein deficiency is present. It has been shown that edema can develop long before the blood concentration reaches this level, a fact which is generally not appreciated by the clinician. It has also been observed that when the serum protein level is as low as 1.4 Gm. per cent edema may be absent in the dehydrated or sodium deprived individual. This adds further confusion to the clinical assay of malnutrition.

Protein inadequacy may be both quantitative and qualitative. If the protein is deficient in tryptophan pellagra may develop at the level of niacin intake, at which a complete protein would prevent its development.

The biomicroscope has been successfully used as an aid to the diagnosis of nutritional disturbances. The technic is simple in that the tissues under question are studied in situ through a binocular microscope. The illumination is intense and focused sharply.The slit lamp of the ophthalmologist is easily adapted for this use. In the hands of the trained observer, the technic yields a great deal of information otherwise unobtainable. The interpretation of the information and its usefulness is still being disputed. Many maintain that it is not as objective a technic as they would like.

Perhaps one of the most useful technics, and the least specific, is the study of the small bowel by means of the roentgenogram. The importance of this, in spite of the lack of specificity, requires a somewhat detailed description of the findings and the interpretations (see Chapter 5).

The roentgen ray studies of the small bowel patterns give contributory evidences of nutritional inadequacies. The abnormalities are not specific for nutritional disorders. The presence of a *Strongyloides* infestation may result in changes similar to those seen primarily due to malnutrition. Allergies may set up the same manifestations, as does the administration of adrenalin. Granulomatous lesions such as the jejuno-ileitis syndrome cannot be differentiated by this procedure. Lymphosarcoma, Hodgkin's disease, and even amyloidosis simulate the same small-intestine patterns when studied by roentgen ray.

The abnormalities vary considerably with the duration and intensity of the nutritional disturbances. The motility of the intestines is influenced by the nutritional inadequacies of the diet. With the development of the abnormalities there is first a hypermotility. The ingested barium may rush through the jejunum so fast as never to outline it satisfactorily. It may be seen in the lower ileum and cecum as early as ½ hour after ingestion. In this early phase, the lumen of the small intestine is usually reduced in width. As the condition progresses this hypertonicity of the bowel gives away to an atonicity. The barium may not reach the lower ileum and cecum for six hours or longer. The lumen of the intestines now appears larger than normal. The atonic loops are distended.

The spasticity of the muscle of the small intestines coupled with what may be a disordered reflex interfere with the usually coordinated intestinal progressive peristaltic waves. The picture seen under the fluoroscope is frequently described as puddling of the barium or segmentation of the intestines. One sees fusiform masses of barium in isolated units. If the gut is in an atonic phase these may be larger rounded masses. In the hypertonic phase the segments may be narrower than the normal lumen and smaller in size. The lower jejunum and first part of the ileum are usually first affected and the last to return to normal under therapy.

After the bulk of the barium has passed into the ileum and beyond, one frequently sees an irregular scattering of residual barium in the jejunum. These barium masses are small, irregular in size, shape and distribution.

Part II

THE NUTRIENT ELEMENTS

Chapter 7

PROTEIN MALNUTRITION

Robert Elman and Paul R. Cannon

THE significance of proteins in nutrition was first recognized in 1839, when Mulder extracted from plant and animal tissues a nitrogenous material which he regarded as the most important substance in the organic kingdom.[8] For this material he proposed the name protein, meaning that it was a "primary substance" (from *proteios*, of first importance). Largely because of Mulder's work, attention for the next sixty years was directed principally to the role of nitrogen in nutrition; and during this period the method of nitrogen balance became a standard procedure for assessing the nutritive value of protein. From the analysis of data secured by this method arose the opposing views concerning the advantages of a high protein or a low protein diet. Thus Voit, as early as 1881, concluded that a man on a daily food intake of 3000 calories needed an average protein intake of 110–120 Gm.;[12] and Voit's idea prevailed for years, despite the demonstration by others that as little as 40 Gm. of protein daily could keep a man in nitrogen equilibrium.

Shortly after 1900 Chittenden[3] started a series of experiments which emphasized the physiologic economy of a protein intake considerably lower than that recommended by Voit. In these experiments he observed that strength and vigor could be maintained for several months on a daily protein intake of 36–40 Gm. and that nitrogen balance could be maintained on a daily intake of 0.6–0.8 Gm. protein per Kg. of body weight. For a 70 Kg. man this would represent a protein intake of 42–56 Gm. per day. Although Chittenden's "low protein" diet was approximately one-third of the diet advocated by Voit, it was actually not much lower than what today is considered optimal for maintenance, namely, 1 Gm. protein per Kg. of body weight. Unfortunately, Chittenden, like his predecessors, thought only in terms of crude nitrogen intake and outgo, despite Voit's earlier observation that gelatin, regardless of its high nitrogen content, still could not serve as a substitute for meat protein.

The current attitude toward protein nutrition began to emerge in 1906, when Willcock and Hopkins first demonstrated the nutritive indispensability of a single amino acid, tryptophan.[14] This observation, followed shortly (1912) by the series of classic experiments of Osborne and Mendel, soon revealed the hitherto unsuspected role of amino acids in nutrition, with particular emphasis upon the significance of tryptophan and lysine as "limiting factors."[8]

Of their many pupils, W. C. Rose, in particular, extended the work of Osborne and Mendel to the present point of view.[10] By ingenuity and persistent effort he and his associates gradually demonstrated the nutritive indispensability of an increasing number of amino acids, culminating in 1935, in the discovery of threonine. With the synthesis of this amino acid, coupled with the synthesis and purification of all the others, it at last became possible to secure good growth, reproduction, maintenance, and nitrogen balance in lower animals, and nitrogen balance in man fed diets adequate in other dietary essentials and containing a mixture of purified amino acids as the sole source of dietary nitrogen. After this achievement, clarification of many puzzling aspects of protein metabolism quickly followed.

Although it is still recognized that without protein life cannot be sustained, it is also recognized now that neither can it be sustained in the absence of other dietary essentials as well. The nutritional role of protein, therefore, centers mainly around its quantitative and qualitative relationship to all the dietary nutrients which determine cellular structure and function in the total assemblage of dietary essentials.

CHEMICAL ASPECTS OF PROTEIN NUTRITION

The "Building Stones" of Protein

It is now agreed that food proteins furnish nitrogen to the tissues; but they do this in the form of amino acids, the so-called "building stones" of protein. These amino acids become available for the building of body protein only following their release from dietary protein in the course of proteolytic digestion. Of the dietary amino acids approximately twenty-two are now known. After absorption from the digestive tract the amino acids and some peptides circulate through the blood and are quickly transformed into body proteins by synthesizing mechanisms located in various tissues. In this synthesis water, calories, vitamins, and minerals play an important part; but the primary function of the amino acids is to supply constructive units for the fabrication of bodily tissue, and these must be furnished daily to the tissues in definite amounts.* Furthermore, they are needed in larger quantities in times of biologic stress, as in disease of various sorts. Without a continuous intake of dietary protein, therefore, optimal growth, reproduction, and maintenance of health are impossible.

Essential and Nonessential Amino Acids

The dietary amino acids are of two kinds: the essential or indispensable, and the nonessential or dispensable. By the former is meant an amino acid which the body itself cannot synthesize, at least rapidly enough to satisfy certain urgent nutritional needs. Of the essential amino acids there are eight or ten, depending upon the mammalian species. Thus for the growing rat there are ten; for the adult rat, nine; and for adult man, probably only eight.[11] The two kinds of amino acids are listed in Table 14.

TABLE 14. ESSENTIAL AND NONESSENTIAL AMINO ACIDS (FOR MAN)

Essential	*Nonessential*
Tryptophan	Histidine (?)
Lysine	Arginine (?)
Methionine	Alanine
Threonine	Glycine
Phenylalanine	Glutamic acid
Leucine	Hydroxyglutamic acid
Isoleucine	Aspartic acid
Valine	Cystine
	Cysteine
	Tyrosine
	Proline
	Hydroxyproline
	Serine
	Norleucine
	Citrulline

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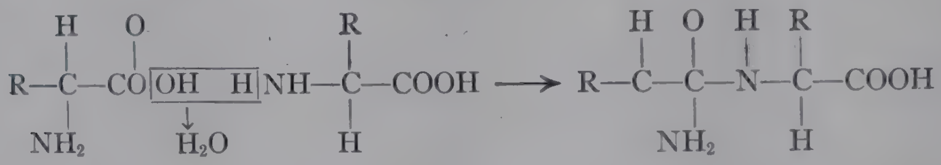
* Indeed there is accumulating evidence that for optimal efficiency all the indispensable amino acids should be available to the synthesizing mechanism practically simultaneously and in proper relationships one to another.[2]

In actual practice, it should be emphasized, the nonessential amino acids are just as important as the essential ones, inasmuch as both are necessary for protein synthesis. While it is true that growth and nitrogen balance may be maintained by the essential amino acids alone, what happens with such an intake is that many of them are transformed to the nonessential type before protein synthesis takes place. This, of course, is a wasteful, unnecessary, and probably time-consuming process. Thus the optimum amino acid mixture is one which contains an adequate supply of both essential and nonessential amino acids, and this, of course, is the case of the composition of all food proteins of high biologic value.

Peptide Linkages

Aggregation of amino acids into protein is brought about by a union of individual amino acids into long polypeptide chains, the product of a chemical reaction whereby so-called peptide linkages result from the union of an amino group (NH_2) of one amino acid with the carboxyl (COOH) groups of another. In the process water is eliminated:



$$\mathrm{R{-}\underset{NH_2}{\overset{H}{C}}{-}\overset{O}{C}O\underset{\overset{\downarrow}{H_2O}}{\boxed{OH\quad H}}NH{-}\underset{H}{\overset{R}{C}}{-}COOH} \longrightarrow \mathrm{R{-}\overset{H}{C}{-}\underset{NH_2}{\overset{O}{C}}{-}\overset{H}{N}{-}\underset{H}{\overset{R}{C}}{-}COOH}$$

Formation of the peptide linkage (—CONH—) requires energy, which with other less well-defined forces tends to hold the amino acids together in large protein molecules. The linkages may be broken by digestive enzymes or, outside the body, by chemical hydrolysis; in either case there is a resultant release of individual amino acids. It is now evident, moreover, that these peptide linkages are being rapidly and continuously opened and closed in normal tissues, allowing a free interchange between amino acids in the dynamic processes of protein metabolism. This concept of protein metabolism has been greatly advanced by the work with isotopes by Schoenheimer and his coworkers and followers. As expressed by him "All of the constituents of living matter whether functional or structural, of simple or complex constitution are in a steady state of rapid flux."

The proteins of various tissues vary not only with respect to their amino acid content but also with respect to their characteristic position in the molecule—hence the almost infinite variety of combinations possible. Despite this great complexity, each mammalian species tends to reproduce its specific proteins with unfailing accuracy, provided that all necessary amino acids are available to the synthesizing mechanisms.

Complete and Incomplete Proteins

The essential amino acids play a predominant part in tissue protein fabrication. Because tissues cannot manufacture essential amino acids from non-essential ones, the former are absolutely indispensable and can be obtained only from proper foods. Some food proteins contain all the essential amino acids and are termed "complete" proteins. These consist principally of proteins of animal origin, including meat, fish, poultry, eggs, milk, and cheese. Other food proteins are less well supplied with essential amino acids and are called "incomplete" proteins, as, for example, those in plants, cereals, legumes, yeasts, fruits, and vegetables. The incomplete proteins in some plants, moreover, may have inadequate quantities of a particular essential amino acid, as for instance, wheat (lysine deficient); yeasts, and some legumes (methionine deficient); and corn (tryptophane and lysine deficient). Incomplete proteins are at times made even more incomplete by bad processing methods, as from overmilling or overheating, in the course of which essential amino acids are discarded in the germ or bran, or are damaged or destroyed by high temperatures or pressures.

Partial or complete amino acid deficiency, so common in vegetable proteins, can often be corrected by using proper mixtures of them. This is possible because these deficiencies in vegetable proteins are practically never due to the absence of the same amino acid. Thus a deficiency in a particular vegetable protein can be corrected by ingesting at the same time another vegetable protein which contains enough of the missing amino acid.

PHYSIOLOGIC ASPECTS OF PROTEIN NUTRITION

In the absence of enough dietary protein to meet all daily metabolic needs, the physiologic processes of growth and maintenance, and the formation of blood and tissue proteins, enzymes, certain hormones, and antibodies cannot be adequately ensured. Moreover, "protein" of any kind is not enough; it should be high-quality protein; and if it is in any way incomplete, it must be blended with high-quality protein or at least a protein which supplies the deficiency if it is to supply to the tissues all the essential amino acids in proper proportions and amounts. The lack of one single essential amino acid may constitute a "limiting factor" and make impossible the effective utilization of the others. Thus a poor protein, such as corn zein, can be no better, nutritionally, than its limiting content of tryptophan; and wheat gluten is restricted in its nutritive potentiality to the extent that lysine acts as a limiting factor.

Whenever one or more essential amino acids are missing from the diet, or when they are supplied in amounts below the continuing bodily needs, catabolism predominates and the individual goes into negative nitrogen balance. This means that more nitrogen is being lost via the urine, feces, sweat, hair, or from wounds and secretions than is being supplied by the food. If the ensuing tissue loss is not counteracted by protein repletion death eventually becomes inevitable. In infection, after severe trauma, etc., the so-called "toxic destruction of protein" increases the "catabolic phase" and thus aggravates the problem of repletion.

Without an adequate intake of good protein, therefore, tissues cannot maintain their physiologic efficiency, a condition which is known as protein deficiency, varying in severity and degree, depending upon the extent of tissue loss and tissue replenishment by dietary protein. In starvation due to a continuously inadequate protein intake, the tissues gradually waste away, as the result, presumably, of their conversion into energy. Protein deficiency may occur, also, because of the presence of so-called "conditioning factors" to be discussed shortly in more detail. The effect, however, is essentially that of no protein or at least of too little protein in the diet.

Relationship of Other Food Elements to Protein Synthesis

Tissue proteins cannot be formed from amino acids unless sufficient calories are available to supply energy for many purposes, including the formation of the peptide linkages. Hence when the caloric intake is below maintenance levels, some dietary or even tissue protein may be converted into glucose: the process of gluconeogenesis. Such a change is physiologically unsound, first, because protein is a costly source of energy; and, second, because the function of food protein is to supply amino acids for constructive purposes rather than for energy; the latter can be obtained more economically from fat and carbohydrate. Furthermore, in the transformation of amino acids into protein there is evidence that energy from carbohydrate and fat promotes the more efficient functioning of certain enzymes and vitamins concerned in the processes of tissue synthesis. Among these vitamins, A and D are essential for growth of soft tissues and bone respectively, and for the fabrication of various tissue-proteins those of the B complex seem to be particularly important. Among them are riboflavin, thiamine, niacin, pyridoxine, biotin, pantothenic acid, and folic acid. Although the precise role of minerals is but incompletely understood, there is reason to suppose that they, too, are necessary for purposes of tissue synthesis.

Thus, modern nutrition stresses the concept that in the process whereby amino acids are built into protein molecules, calories, vitamins, and minerals are all essential. An optimal diet, therefore, ensures physiologic fitness only if it supplies these dietary constituents as well as amino acids both in time and amounts adequate for the qualitative and quantitative needs of all the tissues. The therapeutic objective is to accomplish this for each nutritional situation. In the normal individual the problem is well understood; in patients, therapy is sometimes complex and poorly understood. Many of these details will be discussed later.

PROTEIN REQUIREMENTS

Protein requirements vary in health and disease from day to day and at different ages. Highest in infancy, they also remain high in adolescence and youth. They tend to stabilize in adulthood but become elevated in biologic emergencies such as pregnancy, lactation, infection, burns, trauma, and hyperthyroidism. Opinion has differed widely even as to the normal daily protein needs, particularly for maintenance. For the adult these have been estimated as ranging between 25 Gm. and 125 Gm. per day. Some assume that any amount of protein above minimal needs is superfluous; others maintain that a reasonable margin of safety is advisable, even at the cost of wastefulness. Today an effort is being made to ascertain the optimal intake of protein in a diet otherwise adequate. Usually followed are the *Recommended Daily Dietary Allowances* of the Food and Nutrition Board of the National Research Council. Here the recommendation for adequate maintenance of an adult is 1 Gm. protein per Kg. of body weight. For women slightly more is recommended, and as much as 1.5 Gm. per Kg. in pregnancy and lactation. For infants, from 3–4 Gm. per Kg. is advised. For further details see Appendix Table A.

The difficulty with these allowances is, however, that they presumably apply to good protein, yet not all dietary protein is "good" protein, particularly when a considerable proportion comes from overmilled or overprocessed foods, as, for example, white flour, corn grits, and toasted or puffed cereals. More important, however, is the fact that these allowances, in general, are for maintenance only; many patients are suffering from protein deficiency, and it is now known that the protein needs for depleted tissues are considerably augmented. There is a great need for information as to the quantitative needs for effective tissue repletion, but data are still meager. Finally, there is but little information concerning essential amino acid requirements, either for maintenance or for medical or surgical episodes. Until these have been secured, precise standards cannot be established.

PATHOLOGIC CONSEQUENCES OF PROTEIN DEFICIENCY

Protein deficiency may develop (1) because of a totally reduced intake of all dietary amino acids, as in starvation, (2) because of an increased loss of blood and tissue proteins, or (3) because of a faulty assimilation or synthesis. In the first instance there is usually a concomitant reduction in caloric intake as well as of vitamins and minerals. Because of a calorie deficit, tissue proteins may be drawn upon to supply energy, thus aggravating the degree of protein or amino acid deficiency. As a consequence atrophy of various organs ensues and may be associated with such pathologic effects as asthenia, weight loss, anemia, leukopenia, hypoproteinemia, impaired lactation, decreased capacity to form immune substances, decreased resistance to infection, slow wound healing, lymphoid depletion, and a reduced ability to fabricate certain hormones and enzyme systems. Fortunately, these abnormalities are ordinarily reversible, requiring only a suitable repletion diet in order to supply food constituents and energy essential for tissue rebuilding.

The second cause of protein deficiency is of two types: (1) that accompanying an excessive breakdown of tissue protein, and (2) that resulting from a loss of blood proteins. With reference to the first, some tissue breakdown goes on normally, because of the fact that protein molecules undergo a steady degradation. However, the normal rate of tissue protein breakdown becomes accelerated during infection, after injury of various kinds, and after operation. The amount of tissue protein which may be lost in this way, the so-called "toxic destruction of protein," may at times be equivalent to between two and three pounds of muscle tissue a day. Such a large loss does not occur often, but it helps to explain the rapid fall in body weight in sick patients. In the second type, protein may be lost, also, directly from the blood stream, and in a variety of ways. For example, in hemorrhage, large amounts of protein may be lost. Thus a liter of blood from a torn artery represents a loss of 140 Gm. of hemoglobin and about 60 Gm. of plasma protein, or a total of 200 Gm. of protein. Whole blood and plasma are also lost into tissue spaces or into body cavities following trauma, infection, or inflammation. Inflammation of the lungs or peritoneal cavity or of tissues in general may lead to extravasation of whole blood or plasma which is later broken down and excreted and thereby lost from the body just as effectively as if it had escaped from an injured artery. The amount lost in this way has not been accurately calculated, but it is probable that as much as 100 Gm. of protein may be lost. Unlike the single loss from hemorrhage, leakage through injured or inflamed capillaries may persist for several days. Protein may be lost, also, from surface wounds or burns. This lost protein can be collected and measured; in severe cases several observers have found this to amount to as much as 50 Gm. per day. Albuminuria may also be a significant source of loss, amounting at times to 25 Gm. a day. It is evident, therefore, that under pathologic conditions the loss of protein may be large, up to several hundred grams a day.

The third cause of protein deficiency deals with conditions in which, although there is no actual loss of protein, metabolism is so disturbed that dietary protein may not be digested and absorbed, or absorbed protein cannot be synthesized into plasma protein or hemoglobin. Thus in nephrosis, in some cases of cirrhosis of the liver, and in certain anemias, it is probable that there is an impaired ability of the body to use amino acids for the synthesis of plasma albumin or hemoglobin. A persistently low concentration of plasma albumin or of hemoglobin, despite the administration and assimilation of adequate protein nourishment and iron, can be explained only by such an assumption.

Clinical Causes of Protein Deficiency

Protein deficiency may occur, as already mentioned, because of an inadequate protein intake, due either to a reduced food intake or a too great dependence upon a qualitatively inferior protein, as, for example, corn grits; this is often referred to as a primary deficiency. Protein deficiency may also arise secondarily because of so-called "conditioning factors"[10] reviewed by Jolliffe in Chapter 1 (pp. 22-31).

PRIMARY PROTEIN DEFICIENCY

Failure to eat enough good-quality protein to satisfy the daily protein needs leads to tissue-protein loss. Ordinarily this is due to a low caloric intake, as during periods of famine, or because of poverty, insanity, ignorance, dietary faddism, and the like. The consequences of a caloric and protein deficiency are, in general, a general retardation of all bodily functions. (For further details see Chapter 9 on starvation, which, to a considerable degree, is a manifestation of protein deficiency.)

SECONDARY PROTEIN DEFICIENCY

In this form of protein deficiency there is inadequate utilization of protein by the tissues, despite an adequate intake, because of interference with proper digestion, absorption, and assimilation. Conditioning factors may be due to (1) obstructive lesions of the gastrointestinal tract, as in cardiac spasm or stenosis, carcinoma of the esophagus or stomach, chronic intestinal obstruction, or pyloric stenosis; (2) the accelerated passage of food through the intestine, as in diarrhea; (3) impaired digestion, as in the case of achylia gastrica, or pancreatic steatorrhea; (4) impaired assimilation and utilization, as in the presence of hyperthyroidism, fever, infection, hepatic disease, and the like.

When conditioning factors prevent the proper utilization of protein, even when ingested in dietary amounts, conditioning factors become of prime importance; and until they have been eliminated one cannot hope to attain adequate protein nutrition even in the presence of a good dietary intake.

DEGREE OF PROTEIN DEFICIENCY

Protein deficiency can be expressed quantitatively in terms of unreplaced losses, i.e., negative nitrogen balance. Any patient in whom an inadequate amount of protein is absorbed and metabolized will develop a protein deficiency whose severity will vary with the length of time or extent of the deprivation, as compared with the amount of protein lost either from breakdown of tissue or from actual loss of blood. This deficiency will, of course, be cumulative; and if one knew the exact intake and output, one could calculate the deficiency in terms of grams of protein. From many observations it has been found that on the basis of deprivation of protein alone the body may need from two hundred to three thousand grams of protein to restore the tissues to normal.

CLINICAL MANIFESTATIONS OF PROTEIN DEFICIENCY

Protein deficiency may produce severe signs and symptoms when the deficit is acute, or it may produce very few signs indeed when the loss is slow. For example, the sudden loss of protein, as in hemorrhage, will be followed by surgical shock, which, although seldom regarded as an acute protein deficiency, actually should be looked upon as such. Similar manifestations due to the great and rapid loss of plasma protein in burns will also produce severe manifestations, including shock.

When the protein deficiency is due to protein deprivation alone, without acute loss, the first signs and symptoms may be very slight, yet detectable. For example, it is probable that even twenty-four hours of protein deprivation may be associated with some degree of malaise and weakness. As protein deprivation increases the asthenia may become more prominent. After weeks or months, however, tissue depletion becomes so marked that the following signs and symptoms may become conspicuous.

1. Loss of Weight

Loss of weight is an obvious indication of malnutrition in general and protein deficiency in particular. However, loss of weight in itself must be evaluated carefully inasmuch as there are at least two ways in which body weight may be influenced independently of protein deficiency. In the first place, loss of weight may be due merely to loss of adipose tissue as, for example, after a reducing diet. On the other hand, with a caloric intake greater than his needs and with an inadequate protein intake the patient may gain weight as fat while developing a protein deficiency.

Body weight will also be affected by a loss or gain of body water. This, in contrast to what has already been said about fatty tissue, is directly connected with protein deficiency. For example, nutritional edema causes a gain in body weight because of retention of water and is a well-known manifestation of severe protein deficiency. Conversely, loss of edema fluid leads to a fall of body weight through diuresis and is a manifestation of improvement in protein deficiency. This leads to an apparent paradox in that a patient who is on a good protein intake and is therefore correcting his protein deficiency may lose weight for several days as the result of the loss of excess body water before he begins to lay down tissue protein and gain weight. The physician must not be alarmed, therefore, at such a loss of body weight because it is the first step in the correction of the protein deficiency. By contrast, a gain in body weight while a patient is on a protein-deficient diet should be viewed as a bad sign because it means that the patient is retaining water rather than building tissues.

2. Skin Changes

In severe protein deficiency the skin loses its soft, moist, elastic character and assumes a dry, scaly appearance. It withstands trauma poorly, and bed sores often appear at points of pressure, such as over the sacrum and elsewhere. Slight wounds often fail to heal normally or even progress with ordinary care or tend to become seriously infected. Cellulitis is common and paronychia appear, assume a chronic character, and fail to heal following adequate drainage. Simple abscesses fail to respond to incision and drainage. Part of these changes is due to a lowered resistance and part to impaired wound healing.

3. Reduced Resistance to Infection

Leukocytes, lymphocytes, and antibody protein are all dependent upon an adequate intake of dietary protein for their structural and functional needs. A severe and prolonged protein deficiency, therefore, might be expected to lead to marked depletion of the bone marrow and lymphoid tissues and of the capacity of the antibody mechanism to fabricate antibody protein. Accumulating evidence indicates that this is the case[1, 2] and that such protein depletion lowers resistance to bacterial infection. It has long been observed that tuberculosis tends to increase in incidence and severity in times of famine and that severely undernourished persons are less resistant to other types of intercurrent infection. Usually the protein deficiency is a part of starvation, where, because of inadequate caloric as well as protein intake, there is a loss of protein stores and an impairment of normal protein synthesis. When the protein deficiency becomes severe enough to be associated with edema, the chances of intercurrent infection are also favored. Any type of developing infection will tend to use up more and more of the cellular and circulating reserves of protein, thus emphasizing the need for adequate dietary repletion.

4. IMPAIRED HEALING

Protein deficiency also tends to hamper wound healing.[5, 7] Thus experiments have indicated a delayed healing of surgical incisions due to lessened tensile strength due to diminished fibroplasia and to a lag in the maturation of reticulum into collagen. In severe protein deficiency, with developing nutritional edema, local edema may also contribute to the lag in fibroplasia as well as to a lowered resistance to local infection.

5. HEPATIC INSUFFICIENCY

Recent experiments have shown that deprivation of protein in the diet, even though all the other nutrients are supplied, leads to definite signs of hepatic impairment associated with depletion of the normal amount of protein in the liver cells. The protective effect of protein on the liver following administration of various hepatic toxic agents has been shown repeatedly. Moreover, the beneficial effects of a high protein intake with various types of liver disease have also been demonstrated. It is obvious, therefore, that not only carbohydrate but also protein helps to protect the liver against injurious agents.

6. NUTRITIONAL EDEMA

Symmetrical tissue edema not due to cardiac or renal disease, manifested usually first in the scrotum or labia, is nearly always due to a protein deficiency. This is often, although not always, associated with a marked lowering of the albumin concentration in the blood plasma. Nutritional edema occurs not only in the visible tissues but also in the viscera. Of especial importance is that which occurs in the gastrointestinal tract. Here the edema fluid may lead to obstruction at the sites of surgical anastomosis and this may be misinterpreted by the surgeon. Even in nonsurgical cases mucosal edema may interfere with normal digestive functioning and produce such symptoms as distention, diarrhea, or vomiting. In the severer cases of malnutrition the gastrointestinal tract may even be unable to retain water, as was demonstrated during the severe famines of India in recent years and in the concentration camps of Europe during the Second World War.

Nutritional edema, while related to a depletion of the albumin fraction of the plasma, is conditioned also by other factors. Thus it is not apt to occur in malnourished patients who are kept at rest in bed. Only when they get up and exercise is it likely to be precipitated. The ingestion of large amounts of fluid also tends to precipitate the development of the edema, particularly if the fluid contains considerable amounts of salt.

7. Laboratory Findings

One of the most helpful laboratory procedures for the diagnosis of protein deficiency is the measurement of concentration of hemoglobin and plasma protein. Deprivation of protein will lead to anemia as well as to hypoproteinemia. Anemia is, of course, relatively easy to detect. Measurements of the plasma proteins are also easy to carry out. However, the actual interpretation of these findings is not always easy inasmuch as malnutrition is frequently accompanied by a diminution in extracellular space volume, especially that of the circulating blood. Under these circumstances the total amount of the hemoglobin or plasma protein circulating in the blood stream may be greatly reduced with little or no change in concentration. Thus a normal value may give a false sense of security. It should be emphasized, therefore, that a normal value does not exclude the existence of either hemoglobin or plasma-protein deficiency, at least until it is determined that the blood volume is normal. However, when a low value is found, one may be sure, of course, that the deficiency exists.

Liver biopsy may also reveal changes characteristic of protein deficiency. Thus if the patient is well nourished the cytoplasm of the hepatic cells will be vacuolated and well filled out, whereas if the patient has been starved the cells will be small and contracted, with, in some stages, infiltration by large droplets of fat.

DIAGNOSIS

The diagnosis of protein deficiency usually is relatively easy on the basis of the clinical and laboratory findings as outlined. However, it can usually be made, also, upon the history alone, particularly in the mild cases where there are few laboratory or clinical signs. Indeed this is often the only way in which the diagnosis can be made. All that is necessary is to know what the protein intake has been. Any patient who has ingested little or no protein in his diet will inevitably develop a protein deficiency. Inquiries should therefore be made concerning the protein intake in recent weeks and particularly of the intake of proteins of known high biologic values such as milk, meat, and eggs. The history will also be of value in detecting diseases or conditions which are known to lead to abnormally high protein losses. For example, a long-continued infection may lead to a large loss of nitrogen in the urine. Inflammatory lesions, operations, injuries, conditions which have led to hemorrhage, all will produce protein deficiency, as already mentioned.

The early diagnosis of protein deficiency depends, therefore, upon a good nutritional history and a knowledge of the conditions which lead to loss of protein rather than any particular laboratory procedure or measurement known at the present time which can be carried out by the average physician. This should be emphasized because protein deficiencies can nearly always be suspected and corrected without resorting to complicated methods of laboratory examination.

TREATMENT

Prevention of Protein Malnutrition

Nowhere is it truer than in relation to protein deficiency that an ounce of prevention is worth a pound of cure. The correction of severe protein deficiencies is difficult, and, indeed, at times may prove impossible without special methods. Moreover, the amount of protein which must be given to correct a chronic prolonged deficiency is often so great that practical difficulties are inevitable. By contrast, the prevention of protein deficiency is simple because relatively little protein is needed, and it can often be administered with ease. Entirely apart from this, the assurance of a good protein intake will prevent many clinical manifestations which are associated with protein deficiency, and thus many complications during disease will be prevented. Moreover, the prevention of protein deficiency will greatly shorten the period of convalescence, a fact of great economic significance in the care of the sick.

Prevention of protein deficiencies can be achieved, first, by education of physicians and laymen alike to insist upon an adequate intake of protein from the beginning of any disease. If the patient does so himself before he comes to the physician, protein deficiencies will be avoided. In many cases, unfortunately, the physician himself is at fault because he fails to realize the importance of protein intake when he is actively treating the patient. Too often he awakens to this realization only after the patient has failed to improve and, indeed, has developed obvious signs of malnutrition. The lesson for the physician, therefore, is to take active measures to prevent protein deficiencies from developing while the patient is under his care. This is the least he can do. If the patient already suffers from protein deficiency when he is first seen by the physician, the problem is, of course, much greater, and at times it may be impossible to correct the protein deficiency itself until the disease is cured. However, it should not be allowed to become greater.

In summary: Prevention of protein deficiency depends to a large extent upon the attitude of the physician toward the food intake of the patient from the first day that he comes under his care, and upon his knowledge of and attention to the details of such intake. In the following discussion two methods of administering protein will be discussed, the oral method and the parenteral method.

Oral Administration of Protein

In patients who do not vomit and have a normal gastrointestinal function, the oral administration of protein is obviously the best, the cheapest, and the most efficient method of providing protein for the body. This must be emphasized because the great extension of parenteral methods may sometimes lead to their unnecessary use when the oral route is just as effective. However, the physician cannot simply order a diet and assume that this in itself will solve the nutritional problem. He must realize that sick patients frequently do not eat the diet which is prescribed. It is not the ordering of the diet which is important, but its actual consumption by the patient. The physician should often be present at the time the diet is offered to the patient, or shortly thereafter, so that he may see for himself just how much is actually eaten. He will be surprised to learn how little of the diet is consumed and will thus be brought face to face with a startling but too prevalent phenomenon: that many patients are actually starving in the midst of plenty. Yet without special observation the physician will not know that the patient is not consuming the diet which has been prepared for him, which instead appears in the waste can.

The physician's first responsibility is to determine just what the patient needs, and to communicate to the patient the importance and the necessity of consuming an adequate diet. Anorexia is usually the reason most patients do not eat all of their diets. Anorexia, however, must not be accepted as an inevitable symptom, but something which can be combated by an active therapeutic program. Often anorexia can be met in a simple way. The word of the physician, for example, will sometimes serve as a sufficient stimulus. The patient may be told that appetite in the sick is a luxury, and that while he is sick he had better eat with or without appetite, and that this is important in order to prevent malnutrition during his illness. Thus the physician ordering a normal diet will, in a few cases, be gratified to find that the diet is actually consumed, and if this is possible, it is the simplest method known of preventing a protein deficiency. The preparation and serving of food are of paramount importance and too often neglected.

If the patient is malnourished at the time of entrance and needs more protein, the same principles apply. Instead of a normal diet, a high protein diet containing up to 150 Gm. of protein may be ordered. But here again the physician must assure himself by actual observation and consultation with the patient as well as with the nurse and dietitian that the ordered diet is actually consumed. Only under these circumstances will the protein deficiency be corrected or prevented. Full cooperation between all personnel is essential for this objective, but in the simple cases will be quite effective and will solve the therapeutic problem without a resort to other devices.

SPECIAL DEVICES

In many patients, simple methods fail or the necessary supervision and scrutiny is not possible or sufficient. Moreover, many patients are so sick that they will not or cannot eat a normal diet, particularly when its amount is increased. Two procedures may be followed to meet this situation. In the first place, the physician may reduce the bulk of the diet by sacrificing caloric intake without reducing the protein intake. This is very effective because the caloric portion of a normal diet actually comprises about 80 to 90 per cent of its bulk. This procedure is justified in patients who have a moderate to large amount of adipose tissue, because the deficiency in calories will be compensated by the burning of the patient's own fatty tissue. In the obese this in itself is an advantage, but in any case it makes the administration of protein in sufficient amount much easier because it reduces the total bulk of food which is given.

The second procedure is the employment of liquid rather than solid food. This offers the advantage that many sick patients will swallow liquid with slight difficulty, whereas they may rebel at the need of masticating solid food.

Both objectives can be reached by providing a high-protein liquid drink which may be made up in a variety of ways. The simplest is to utilize skimmed milk powder which contains by weight 35 per cent protein and 55 per cent carbohydrate. To this may be added pure protein in the form of casein. The powder is added to milk or water, flavored, and mixed thoroughly. Eggs or egg powder may also be added, although in the author's experience they may impart a taste to which some patients object. The use of meat products would be an advantage because of the added flavor and variety, and there are meat products available in almost liquid forms that may be tried.

The following is a high-protein liquid diet which has been used at the Barnes Hospital in St. Louis for several years, is palatable, convenient, and relatively inexpensive.

1	qt. milk (whole or skimmed)
135	Gm. dried skimmed milk powder
70	Gm. casec
15	Gm. cocoa
45	Gm. sugar

Make paste of dry ingredients. Add to milk and beat with egg beater until lumps are dissolved. Heat slightly.

Approximate protein content 1 Gm. to 10 cc. Vitamins, especially ascorbic acid, may be added. From one to four glasses a day may be ordered.

A high-protein liquid drink, as outlined above, has the added advantage that it can be ordered as medication rather than as food. In this way the physician is assured of at least a minimum intake which in general may be set at 100 Gm. protein and 100 Gm. carbohydrate. This means about one quart of the above mixture. It is unlikely that this minimum or basic intake will permit much protein deficiency from developing, and indeed, in many cases it will be followed by at least some degree of correction of protein deficiencies which are present. However, this minimum intake should be increased as soon and as much as possible. It may be increased by adding other foods in the form of eggs, custards, junkets, ice cream, or any type of regular food placed on the tray. Indeed, the physician will often find that after a few days intake of this minimum diet the patient's appetite may be so improved that he will eat without difficulty more and more of the regular diet, and indeed, in many cases can soon be eating and chewing beefsteak.

TUBE FEEDING

A few patients with a normal gastrointestinal tract will refuse to swallow, and the passage of a tube into the stomach may then be justified. It is also justified to assure an adequate intake when adequate supervision of normal eating is impossible.

Tube feeding by the passage of a catheter into the stomach through the mouth or nose should always be looked upon as a temporary expedient. The patient should be told this ahead of time and also that after a few days it may be removed when normal oral feedings are started again. After one or two tube feedings the patient will often prefer to take his fluids by mouth. In any case, a small rather than a large tube should be employed. A size 12 is ample to permit the introduction of not too thick liquids. New plastic "polythene" tubes of even smaller caliber are now available and have been used fairly extensively. They are far less irritating to the mucous membranes than the more rigid rubber tubing. Other patients who have a gastrostomy or jejunostomy will also require tube feeding. Tube feeding offers little difficulty except, of course, that the diet must be in liquid form. The high protein drink mentioned above can be readily applied. It must be emphasized, however, that when a tube is passed into the stomach, gastric distention must be avoided in order to prevent regurgitation and aspiration. This is easy to prevent if the feeding is given at intervals and the contents of the stomach are aspirated before additional fluids are administered. A constant drip carries with it the danger of gastric distention unless measures are taken at definite intervals to make sure that fluid is not accumulating in the stomach because it is being given at a greater rate than it is leaving the stomach.

Tube feeding readily permits the use of hydrolyzed rather than whole protein. The advantages of hydrolyzed protein will be discussed under the next heading.

Hydrolyzed Protein by Mouth

Many preparations of hydrolyzed protein have become available in the past few years and may be given as oral feedings in place of whole protein food, thus sparing the body the need for digestion.

The indications for the use of hydrolyzed protein are as follows: (1) Extremely malnourished patients in whom much whole protein provokes digestive disturbances. In many such patients much larger amounts of protein food can be given as hydrolyzed than as whole protein. (2) Patients requiring jejunal feedings. This includes feeding either through a catheter placed directly into the intestine at the time of operation, or through a nasal tube passed across the stomach into the jejunum after gastrectomy. (3) Patients with peptic ulcer. Hydrolyzed protein has been used in the medical treatment of patients with peptic ulcer with reportedly good results. The amino acids, being more of a buffer than whole protein, combine with acid readily. Hydrolyzed protein, moreover, probably involves less gastric motility since digestion is spared. (4) Allergic patients. By supplying a purified diet containing amino acids elimination diets may be investigated without starvation.[15] In infants allergic to milk, hydrolyzed protein has also been successfully used.

Not all of the many preparations of hydrolyzed protein on the market can be recommended. The physician should demand that their composition of essential amino acids be adequate. This is readily shown by the ability of the preparation to support normal growth in immature rats or to produce weight gain in protein-depleted adult rats when fed as the sole source of protein. At least 50 per cent of the hydrolyzed protein, moreover, should consist of single amino acids. Only when this is true will the preparation spare the need for much further digestion.

Most preparations of hydrolyzed protein are not palatable and will be ingested only when presented to the patient properly. The attitude of the physician toward this form of protein administration is extremely important, and too great sympathy with the patient on account of the bad taste will usually lead to difficulties. When presented with the preparation as a form of medication, most patients will accept the bad taste in good spirit. Patients will object much less to the bad taste of medicine than they will of food. A simple method for the administration of large amounts of hydrolyzed protein is as follows: 20 Gm. each of the hydrolyzed protein powder and dextromaltose are added to two separate small jars of about 200 cc. capacity. About 100 cc. of water is then added and each of the mixtures shaken. The patient then drinks very rapidly the hydrolyzed protein solution, followed by the solution of dextromaltose as a "chaser." If this is repeated every hour for twelve hours, the total intake will be 240 Gm. per day, which is a large intake. As much as 300 to 400 Gm. a day have actually been taken and assimilated by many sick patients. For short periods of time this method of therapy can be recommended and probably has a place in the treatment of certain patients before they are able to take a full normal diet. Adequate vitamins must also be given.

The bad taste of hydrolyzed protein is, of course, obviated when it is used in tube feeding. Many physicians have found its employment in this way an advantage over the administration of usual tube feedings containing whole protein. Many have combined hydrolyzed protein with milk and found the mixture of great value in increasing the protein intake in malnourished patients in whom rapid nutritional restoration is desired.

PARENTERAL ADMINISTRATION OF PROTEIN

It is sometimes necessary to administer protein parenterally, particularly by intravenous injection. While this represents a great advance in therapy, it must only be used when definitely indicated and for as short a period as possible. This must be emphasized because all parenteral injections are expensive, inconvenient, unpleasant, and, when given intravenously, not without danger. Their use when indicated will, however, lead to great improvement in the care of patients and to a more rapid restoration of the patient so that he may then take all of his food by mouth.[4]

There are two ways in which protein may be given parenterally: (1) whole blood and plasma transfusions in conditions primarily associated with protein deficits in the blood itself; (2) amino acid mixtures (as such or as hydrolyzed protein) as a source of food in patients whose gastrointestinal tract cannot or should not be used.

WHOLE BLOOD AND PLASMA TRANSFUSIONS

The intravenous injection of whole blood permits the injection of both plasma protein and hemoglobin and is primarily indicated for the correction of such deficits in the blood resulting particularly from severe hemorrhage. Whole blood may be lost either extensively or in tissue trauma or other internal injuries where there is no obvious external hemorrhage. A deficit in hemoglobin is also seen in many inflammatory conditions in which the transudate contains red cells. Certain types of infection also lead to anemia, although the mechanism is somewhat different. Whole blood will be useful in all these conditions.

There are two general *indications* for the parenteral administration of protein. The first represents the replacement of acute losses of hemoglobin and plasma protein which follow hemorrhage, extravasation, etc. Whole blood or plasma transfusions are widely used for this purpose. While it is true that in mild cases replacement will occur spontaneously from other tissues and ultimately from food, the process is a long one. By immediately injecting the lost elements, more rapid convalescence is achieved; moreover in severe losses immediate replacement is often life saving. The second indication for the use of parenteral protein is primarily nutritional, i.e., the maintenance of nutritional needs or replacement of nutritional deficits in any condition in which the gastrointestinal tract cannot be used or should be kept at complete rest. In this way starvation can be largely prevented and some deficits corrected in patients who are unable to take any food by mouth. In certain cases the parenteral route may be used as a supplement to oral administration for purposes of accelerating the nutritional rehabilitation of the patient. Whole blood is valuable for supplying hemoglobin, plasma and particularly pure serum albumin for supplying plasma protein. But for the nutrition of tissues in general, amino acid mixtures supply directly the building stones needed for tissue protein synthesis.

Whole blood is also useful in patients in whom the deficiency in the blood is primarily nutritional. This is true, however, particularly for the correction of anemia which is so often seen in depleted patients. Whatever the cause, hemoglobin deficiencies are characteristically easy to correct by transfusions. This is true because red cells given either as such or as a whole blood transfusion remain in the circulation. Unlike plasma protein, which after injection leaves the blood stream and is metabolized in a matter of days, the hemoglobin in the red cells is broken down and metabolized only after several weeks.

The amount of whole blood needed to correct a deficiency in red cells can be predicted. On the average one liter of whole blood will be required to increase the red cell count by 500,000. In the individual case the amount can be readily determined by measuring the red cell count before and after each of several transfusions until the anemia is completely corrected. There is one pitfall, however, and that is the tendency for malnourished patients to have a normal red count while suffering a diminution in the total amount of circulating blood. The absence of a measurable anemia, therefore, does not necessarily mean that the patient does not require a transfusion. Indeed, the red count occasionally will be found to fall after transfusion. This is not necessarily due to additional loss of blood, but may be due to an increase in the total plasma volume.

Plasma transfusions are indicated when the loss from the blood stream has not affected the red cells as, for example, in most burns, intestinal obstruction and peritonitis, pneumonia, and extensive extravasation from wounds. Often the red count will be high; this hemoconcentration has been called plasma dehydration, in contrast to that which follows loss of gastrointestinal fluid by vomiting. The advantage of plasma over whole blood in these cases is that per unit of volume the former contains twice as much plasma protein as the latter. Plasma, moreover, can be given without the need for typing. On the other hand, pooled plasma has at times been shown to be responsible for the transmission of so-called homologous serum jaundice.

The choice between whole blood and plasma rests primarily upon the question of whether whole blood or merely plasma has been lost. In general, a fall in the red count calls for the former, a rise for the latter. In the absence of plasma, whole blood is obviously better than other plasma substitutes such as gelatin. Conversely, when whole blood is not available, plasma is better than other blood substitutes. Recently, purified human albumin has been prepared from plasma as a 25 per cent salt-poor solution and has many advantages over plasma itself. It is as yet not available, however, for general use.

Nephrosis and hepatic cirrhosis are two diseases in which plasma transfusions have been extensively used, not so much to meet losses as to correct deficits in the blood due to an inability of the body to synthesize enough albumin to keep its normal blood level. In a sense this use of plasma is similar to the employment of insulin in diabetes in that its effect is temporary. In certain cases, however, a remission may result from the injection of plasma (or of pure albumin), especially if a high protein food intake by mouth is maintained. Until the cause of hypoalbuminemia in nephrosis and cirrhosis is found, plasma is to be looked upon as merely a symptomatic form of therapy.

TABLE 15. PLASMA VS. AMINO ACIDS AS INTRAVENOUS PROTEIN FOOD

	Plasma	*Amino acid mixtures (hydrolized protein*)*
Cost (per gram)	$1.75	$ .04
Reactions	2.0%	0.8%
Sodium Chloride† Content (Gm./L.)	9	2
Sodium Citrate Content (Gm./L.)	10	0
Metabolism	Delayed	Immediate

* Amigen solution (includes glucose and salt)
† Including bicarbonate

In contrast to their value for the replacement of blood losses or for the correction of anemia, whole blood (or plasma) as a source of parenteral protein food is both expensive and unphysiologic (see Table 15). Tissue protein is normally synthesized from amino acids presented to it by the blood from the portal stream after absorption from the gastrointestinal tract. Plasma protein presented to the body as a whole blood or plasma transfusion must undergo a metabolic change, presumably to amino acids. This is possible by the action of tissue enzymes which act on the injected protein molecule and prepare it for assimilation by the various tissues of the body. Injected plasma protein has long been known to leave the circulation, but its fate thereafter is still somewhat obscure. Much of it is undoubtedly reformed into tissue protein. On the other hand, the fact that much of it does not remain in the blood explains why it is so difficult with transfusions alone to correct the plasma-protein deficiency so often seen in malnutrition. As already mentioned, this is not true of hemoglobin deficiencies which are readily corrected by the injection of red cells.

While of undoubted value in the therapy of protein malnutrition, the use of blood as the sole source of parenteral protein is no longer justified now that more physiologic methods are available, i.e., solutions of amino acid mixtures.

AMINO ACID MIXTURES

The injection into the blood stream of an appropriate mixture of amino acids (and small peptides) is a physiologic method of alimentation, for this is how ingested protein reaches the tissues. The only difference is that amino acids absorbed from the gastrointestinal tract into the portal system necessarily reach the liver first; apparently this fact does not significantly impair the utilization of amino acids which are injected into the systemic circulation and thus reach all tissues including the liver simultaneously.

Amino acid mixtures for intravenous use have been prepared in pure crystalline form, but as yet are not available for therapeutic use. At present only solutions of adequately hydrolyzed proteins are generally available. These preparations have been extensively used in thousands of patients and seem firmly established in clinical practice. Sufficient study has shown them to be safe and effective. While intravenous injection of amino acid mixtures may provoke a small percentage of untoward reactions, the incidence is no greater than that following blood or plasma transfusions. When properly used they supply to the tissues the building stones of protein, and thus help to prevent protein starvation and may even lead to a certain amount of tissue and plasma protein synthesis. The following is what might be called a simple parenteral diet (as two daily 1-liter injections) in that it supplies nearly all the food elements needed for maintenance, at least for short periods.

Water	2000	cc.
Amino Acids (as hydrolyzed protein)	100	Gm.
Glucose	100	Gm.
Electrolyte (mostly sodium chloride)	5	Gm.

Vitamins separately: C up to 1 Gm.; B_1, 5 mg.; B_2, 5 mg.; niacinamide, 50 mg. Correction of other losses in addition.

The injection of amino acids should be viewed as an essential part of any parenteral nutritional intake. However, all infusions, while important, should be employed only for as short a period as necessary. In most cases but a few days of parenteral injection will be needed, e.g., in preparation for operation and after operation, until the patient is able to take sufficient food by mouth. In exceptional cases a week or more of parenteral feeding may be necessary. On rare occasions, patients have required several weeks of such therapy before they could eat normally.

The duration of each injection must also be as short as possible. Too often intravenous fluids are allowed to run for many hours. In general a normal sized adult will tolerate the infusion of one liter of fluid in two or at the most three hours without circulatory impairment. At this rate solutions of hydrolyzed protein will seldom if ever produce nausea, a symptom which may follow if faster rates are used. With two three-hour injections, a maximum of six out of twenty-four hours need be employed for the usual parenteral fluid administration.

The amount of fluid listed represents a minimal parenteral intake, but in the average case it is adequate. It is obviously unwise to inject more than is absolutely necessary. This minimal amount will not lead to much tissue protein synthesis but will prevent or lessen tissue protein loss. Moreover, it will keep the tissues supplied with readily available amino acids, which presumably improve physiologic function beyond that which is possible when merely water, sodium chloride, and glucose alone are injected.

The advantages of supplying parenteral protein food by means of an adequate mixture of amino acids and peptides are not very different from those which follow the ingestion of protein by mouth. The utilization by the body of the building stones of protein given by injection has been demonstrated by many observers and may be accepted as a physiologic method of nutrition provided, of course, that the preparations used contain enough of all of the essential amino acids. Many of the evils of protein starvation formerly inevitable in patients unable to eat may now be avoided. It is now possible to keep the gastrointestinal tract completely at rest while supplying an almost complete nutritional intake. Many complications of disease, even fatalities, directly or indirectly traceable to protein starvation, may thus be reduced or eliminated and better preoperative preparation and more rapid postoperative restoration achieved.

The contraindications to the use of intravenous hydrolyzed protein are, first, the existence of turbidity in the solution, and, second, the development of an untoward reaction. The former is simple and obvious and is remedied by using only crystal-clear solutions. Of the untoward reactions, only signs of sensitivity such as urticaria, rash, or severe vasomotor changes are absolute contraindications. Serious sensitivity occurs but rarely—probably not more than once in many thousands of injections. Other reactions, particularly of pyrogenic nature, call for discontinuing the injection but are not contraindications to further injections.

BIBLIOGRAPHY

1. Cannon, P. R. "The relationship of protein metabolism to antibody production and resistance to infection," in Advances in Protein Chemistry, Vol. II. New York, Academic Press, 1945.
2. Cannon, P. R. Some Pathologic Consequences of Protein and Amino Acid Deficiencies. American Lecture Series No. 27. Springfield, Illinois, Thomas, 1948.
3. Chittenden, R. H. Physiological Economy in Nutrition. New York, 1905.
4. Elman, Robert. Parenteral Alimentation in Surgery with Special Reference to Proteins and Amino Acids. New York, Hoeber, 1948.
5. Harvey, S. C., and Howes, E. L. Effect of high protein diet on the velocity of growth of fibroblasts in the healing wound. *Ann. Surg.* 91:641, 1930.
6. Jolliffe, N. "Conditioned malnutrition," in *Handbook of Nutrition.* Chicago, A.M.A., 1943.
7. Kobak, M. W., Benditt, E. P., Wissler, R. W., and Steffee, C. H. The relation of protein deficiency to experimental wound healing. *Surg., Gynec. & Obst.* 85:751, 1947.
8. Mendel, L. B. Nutrition: The Chemistry of Life. New Haven, Yale, 1923.
9. National Research Council. Recommended Dietary Allowances. *Report and Circular Series* No. 129, 1948.
10. Rose, W. C. The nutritive significance of the amino acids and certain related compounds. *Science* 86:298, 1937.
11. Rose, W. C. (The Science of Nutrition) The Nutritive Role of the Amino Acids. New York, The Nutrition Foundation, 1946.
12. Sahyun, M. Proteins and Amino Acids in Nutrition. New York, Reinhold, 1948.
13. Schoenheimer, R. The Dynamic State of Body Constituents. Cambridge, Harvard, 1942.
14. Willcock, E. G., and Hopkins, F. G. The importance of individual amino acids in metabolism: Observations on the effect of adding tryptophane to a dietary in which zein is the sole nitrogenous constituent. *J. Physiol.* 35:88, 1906-7.

Chapter 8

CARBOHYDRATE MALNUTRITION*

Samuel Soskin and Rachmiel Levine

THE importance of carbohydrates in human nutrition has varied greatly at different times and in different parts of the world. Grains, fruits, and vegetables are the natural foods which are high in carbohydrate content. Meat, fish, and dairy products are relatively poor in this constituent. Before the development of the modern food processing and distributing industry (and at the present time, in those parts of the world which have not undergone this development) the proportion of carbohydrate in the diet of any region was largely governed by the local flora and fauna. Thus, even now in tropical countries where vegetation is luxurious and the climate leads to rapid spoilage of meat products the proportionate intake of carbohydrate is high. For the obverse reasons, the inhabitants of the Far North always have lived on a diet which consists chiefly of meat and fish. Adequate nutrition is possible at both extremes of this range of dietary variation, provided that the need for calories, essential food factors, vitamins, and minerals is met.[7, 22]

Although there has been some change during the past fifty years in the food sources from which the carbohydrates are derived, the proportion of carbohydrate in the United States' dietary has remained at about 50 to 60 per cent of the total caloric intake. Since certain foods which are high in carbohydrate content are relatively inexpensive, the proportion of carbohydrate in the diet has been greater at lower economic levels than in the more prosperous groups of the population. However, the poorer nutritional status of the lowest income groups is not so much a reflection of their high carbohydrate intake as it is of the particular foods from which they derive their carbohydrates. The highly refined grains and sugars, which have been developed and commercially exploited largely because of their resistance to spoilage, are the cheapest sources of calories generally available. But they have been deprived at the same time of most of the protective elements with which they are naturally associated, so that a *casually selected* high carbohydrate diet is one which is poor in the essential amino acids, vitamins, and minerals.[23]

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THE CARBOHYDRATES IN FOODS

The particular carbohydrates present in the ordinary American diet, the food sources from which these carbohydrates are derived, and the quantitative importance of each carbohydrate in the total intake are indicated in Table 16.

PHYSIOLOGY

DIGESTION[4]

The digestion of carbohydrates starts in the oral cavity. Here the secretion of the parotid gland, which contains an amylase called ptyalin, is mixed with the food and begins the conversion of starch, glycogen, and dextrins into maltose. This digestion continues in the stomach until the hydrochloric acid which is secreted there destroys the amylase activity, and substitutes acid hydrolysis for enzymatic splitting. If continued long enough, the acid hydrolysis can reduce all the digestible carbohydrates to the monosaccharide stage. However, the stomach usually empties itself before this can occur, and the digestion of carbohydrate is taken up by the enzymes of the small intestine, operating in the more alkaline medium which prevails there. The enzymes in the small intestine are: an amylase secreted by the pancreas; and an amylase, a maltase, an invertase, and a lactase secreted by the wall of the small bowel. All these enzymes are capable of reducing the particular sugars which they attack to the monosaccharide stage.

We have accounted for the digestion of starch, dextrins, glycogen, and the disaccharides. Those sugars which are ingested in the form of monosaccharides do not require digestion. All the remaining carbohydrates pass through the stomach and small intestine unchanged. In the large bowel they are subjected to the enzymatic influence of the profuse bacterial flora which is normal there, and may be broken down

Table 16. SOURCES AND END-PRODUCTS OF THE VARIOUS CARBOHYDRATES

Carbohydrates	*Approximate percentage of total carbohydrate intake**	*Chief food sources*	*End-products of digestion*	*Remarks*
Polysaccharides:				
a. Indigestible	3			
1. Celluloses and hemicelluloses		Stalks and leaves of vegetables; outer covering of seeds	—	May be partially split to glucose by bacterial action in large bowel
2. Pectins		Fruits	—	Chemical hydrolysis yields galactose and arabinose
b. Partially digestible	2			
1. Inulin		Jerusalem artichokes, onions, garlic	Fructose	Digestion incomplete; further splitting by bacteria may occur in large bowel
2. Galactogens		Snails	Galactose	
3. Mannosans		Legumes	Mannose	
4. Raffinose		Sugar beets	Glucose, fructose, and galactose	
5. Pentosans		Fruits and gums	Pentoses	
c. Digestible:				
1. Starch and dextrins	50	Grains; vegetables (especially tubers andl egumes)	Glucose	The most important group quantitatively. Usually accompanied by some maltose
2. Glycogen	Negligible	Meat products and sea food	Glucose	
Disaccharides:				
1. Sucrose	25	Cane and beet sugars; molasses; maple syrup	Glucose and fructose	
2. Lactose	10	Milk and milk products	Glucose and galactose	
3. Maltose	Negligible	Malt products	Glucose	
Monosaccharides:				
a. Hexoses:				
1. Glucose	5	Fruits; honey; corn syrup	Glucose	In fruits and vegetables the contents of glucose and fructose depend on species, ripeness, and state of preservation
2. Fructose	5	Fruits; honey	Fructose	
3. Galactose	0	—	Galactose	These monosaccharides do not occur in free form in foods; see under lactose and mannosans
4. Mannose	0	—	Mannose	
b. Pentoses:				
1. Ribose	0	—	Ribose	These monosaccharides do not occur in free form in foods. They are derived from pentosans of fruits and from the nucleic acids of meat products and sea food
2. Xylose	0	—	Xylose	
3. Arabinose	0	—	Arabinose	
Carbohydrate derivatives:				
1. Ethyl alcohol	Variable	Fermented liquors	Absorbed as such	These substances are the products of natural or induced carbohydrate breakdown
2. Lactic acid	Negligible	Milk and milk products		
3. Malic acid	Negligible	Fruits		
4. Citric acid	Negligible	Fruits		

*Calculated from the average dietary of the middle-income group in the United States.

to monosaccharides to some extent. It is possible that minor amounts of carbohydrate are made available in this manner for absorption into the blood stream (see Fig. 10).

ABSORPTION

The monosaccharides ingested as such or arising from the digestion of carbohydrates are practically completely absorbed in the small intestine. Small amounts may be absorbed from the stomach. It is also possible to show that when solutions of monosaccharides are introduced into the large bowel for experimental or therapeutic purposes, some sugar can be absorbed from this portion of the gastrointestinal tract.[3]

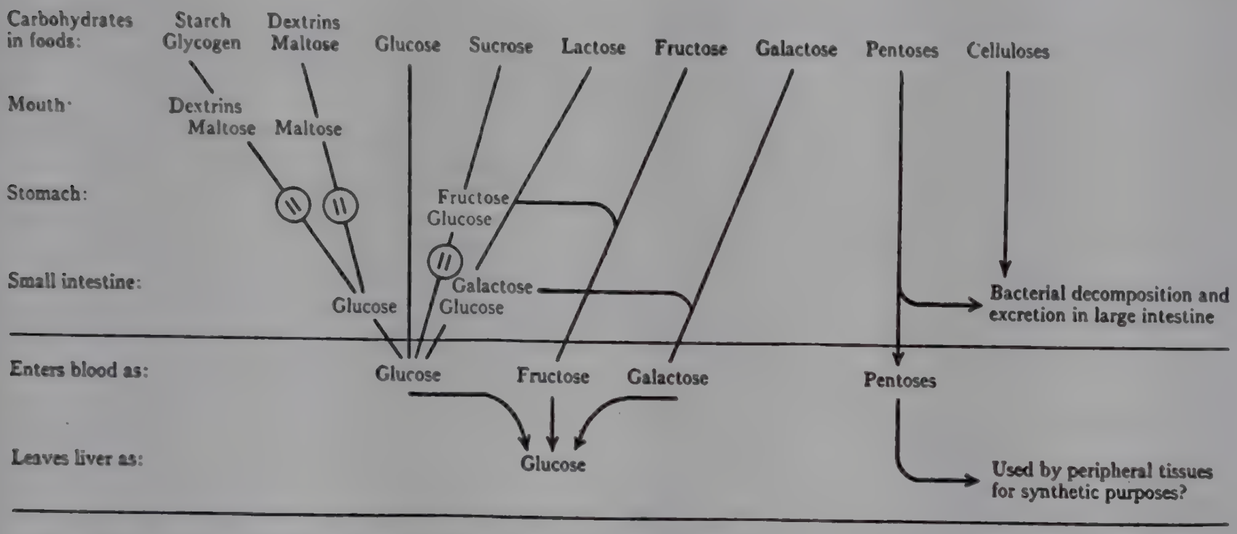

Carbohydrates in foods:
Starch
Glycogen
Dextrins
Maltose
Glucose
Sucrose
Lactose
Fructose
Galactose
Pentoses
Celluloses
Mouth:
Dextrins
Maltose
Maltose
Stomach:
Fructose
Glucose
Small intestine:
Galactose
Glucose
Glucose
Bacterial decomposition and excretion in large intestine
Enters blood as:
Glucose
Fructose
Galactose
Pentoses
Leaves liver as:
Glucose
Used by peripheral tissues for synthetic purposes?

FIG. 10. Products of carbohydrate digestion at various levels of the gastrointestinal tract, and subsequent fate. The ringed "equals" signs indicate that the same products as at the preceding level continue to appear.

Two types of absorption occur in the small intestine: (1) a specific absorption of particular monosaccharides, probably involving a phosphorylation process; and (2) a nonspecific absorption of all monosaccharides, by diffusion resulting from osmotic forces across the mucous membrane. Glucose, fructose, and galactose are absorbed by both processes. Consequently the absorption of these sugars differs in two respects from that of other sugars: (1) they are absorbed more rapidly; and (2) their rates of absorption are largely independent of their concentrations in the intestine.[6]

From the practical standpoint the rate at which a monosaccharide enters the blood stream, when it is eaten as such or arises from the processes of digestion under the usual conditions of feeding, will be governed largely by the rate at which it enters the small intestine and the mixture of foods in the small intestine at the time of absorption. The rate at which the sugar arrives at the small intestine depends largely on the motility of the stomach and the control of the duodenal sphincter, which can be affected by such various phenomena as hunger, emotion, local irritation (including condiments), and the composition and consistency of the food mass after mastication.[4] The food mixture in the small intestine affects the rate of absorption by competition of the various constituents in the mixture for the absorbing surface of the mucosa and, in the case of those monosaccharides which are specifically absorbed, by competition for the available phosphorylating capacity.

Other factors which influence the amount of carbohydrate absorbed in a given individual at a particular time are: (1) the normality of the mucous membrane of the small intestine and the length of time during which the carbohydrate is in contact with it; (2) endocrine function, particularly that of the anterior pituitary gland,[16] the thyroid,[16] and the adrenal cortex;[1] and (3) the adequacy of vitamin intake, especially that of the B complex.[15]

Since the absorption of the important end products of carbohydrate digestion requires chemical activity by the mucous membrane, it is obvious that any abnormality of the mucosal cells might interfere with carbohydrate absorption. Enteritis (inflammation) is a fairly common disturbance of this kind. Celiac disease may represent a more obscure disturbance of a similar nature. However, even when the mucosa is normal, an excessive rate of movement of the carbohydrate along the gastrointestinal tract accompanying diarrheas of various origins may hurry a portion of the ingested carbohydrate into the large bowel before it can be absorbed.

Normal absorption of carbohydrate does not occur in the presence of an anterior pituitary deficiency. This probably depends for the most part upon the secondary hypofunction of the thyroid gland, for the same result may be obtained after removal of the thyroid gland when the hypophysis is intact. Furthermore, the defect in absorption accompanying hypopituitarism may be relieved by the administration of thyroid extract. Indeed Althausen and his co-workers[2] have attempted to make use of this phenomenon as a clinical test of the state of activity of the thyroid gland. They administer a standard amount of galactose by mouth, follow the rise of galactose concentration in the blood, and use the rate of the latter as a criterion of thyroid function.

The adrenal cortex influences carbohydrate absorption through its regulation of the sodium chloride exchange in the body. The absorption of carbohydrate from the intestine is subnormal in adrenal cortical deficiency but can be restored to normal without the use of adrenal cortical extracts if the sodium chloride of the blood is raised to normal levels by adequate salt intake.[1]

Insulin, which has such an important influence on other aspects of carbohydrate metabolism, is without apparent effect upon the absorptive capacity of the intestinal mucous membrane.

Distribution of Carbohydrate in the Body: Its Functions and Uses

In order to understand the distribution of carbohydrate in the body and appreciate its particular functions and uses, it is necessary first to consider the relation of carbohydrate metabolism to that of the other two major foodstuffs.

Protein constitutes 75 per cent of the dry weight of the soft tissues of the body. In view of the recent knowledge as to the protein nature of the tissue enzymes, it is fair generalization to say that the proteins, together with the hormones, vitamins, and minerals constitute the metabolic machinery of the body. In emergencies a certain amount of the protein machinery can be broken down and converted into fuel. However, the amount of body protein which is available for this purpose at any one time is strictly limited, as is also the length of survival which is possible when the body has exhausted its fat stores and is forced to depend upon endogenous protein alone.

Fat differs from protein in that it can be stored in practically unlimited quantities. It is deposited chiefly within layers of connective tissue and not as an integral part of the working organs of the body. When food intake is inadequate to supply the caloric needs of the organism, sufficient fat is mobilized to make up the caloric deficit. In this way practically the entire fat stores of the body can be depleted without detriment to health. Whatever harm accompanies extreme emaciation can be explained by specific deficiencies in the protective food factors incidental to the general restriction in food intake, and by the loss of certain secondary structural functions of fat having to do with heat insulation and the architectural cushioning of organs. Fat is, therefore, primarily a fuel storage material. When food is ingested in excess of caloric expenditure (whether taken in the form of carbohydrate, protein, or fat), the equivalent of the excess calories is deposited as fat in the adipose tissues.

Carbohydrate resembles fat in being a fuel material but differs from fat in that it is an indispensable one. The tissues of the body constantly require and use carbohydrate under all physiologic conditions.[20] Even a temporary fall in the blood sugar below certain critical levels is accompanied by serious disability. Nevertheless, the amount of carbohydrate present in the body at any one time is very small. This amount, if it were not replaced as used, could sustain life for only a fraction of one day. Table 17 compares the total effective carbohydrate content of a hypothetical average normal man with his caloric requirement.

Thus, unless large amounts of carbohydrate are continually ingested with the food, the needs of the body must be met by the conversion of the other foodstuffs into carbohydrate. It is, therefore, the active fuel of the body which is stored only in small quantities and which is taken in or made as required.

TABLE 17. CALORIC EQUIVALENT OF CARBOHYDRATE CONTENT OF NORMAL MAN

BODY WEIGHT, 70 KG.; LIVER WEIGHT, 1800 GM.; MUSCLE MASS, 35 KG.; VOLUME OF BLOOD AND EXTRACELLULAR FLUIDS, 21 LITERS.

	Per cent	*Gm.*
Muscle glycogen	0.70	245
Liver glycogen	6.00	108
Blood and extracellular fluid sugar	0.08	17
Total body carbohydrate		370 Gm.
Caloric equivalent (370×4.1)		1517 cal.
Caloric requirement (sedentary occupation)		2800 cal. per 24 hr., or 116.7 cal. per hr.
Total body carbohydrate could supply caloric needs for (1517/116.7)		13 hr.

CARBOHYDRATE DISTRIBUTION

The carbohydrate of the body is largely present in the form of glycogen in the skeletal, cardiac, and smooth muscles. In these motor tissues it serves as an emergency reserve of fuel; one which can be mobilized more rapidly than carbohydrate can reach these organs through the regular channels. Most of the remaining carbohydrate in the body is found in the manufacturing and distributing system—in the liver as glycogen and in the blood and extracellular fluids as glucose. Relatively small amounts of glycogen are also found in practically all other organs and tissues of the body.

That the greater part of the body carbohydrate is present as glycogen (the polymerized storage form of glucose) depends upon the fact that all the hexoses which result from the digestion of carbohydrate in the intestine, and are absorbed into the blood stream, are converted into glucose. This occurs largely, but perhaps not entirely, in the liver. Similarly, in the postabsorptive state or during fasting when the liver must supply sugar to the blood from the body's own resources, glucose is the carbohydrate which it manufactures from protein and fat. Nevertheless, there are minor amounts of other forms of carbohydrate in most tissues and organs. Among these are special-purpose carbohydrates, which are presumably not used as fuel; for example, the galactose in the galactolipins of nervous tissues, the pentoses associated with the nucleoproteins, and the glucose of the widely distributed glucoproteins. Under special circumstances, such as in the lactating woman, lactose is made in the breast and is present in the secreted milk. Finally, there are a number of degradation products of glucose, such as the hexose and triose phosphates, which are caught in transit as the glucose is utilized.

TABLE 18. DISTRIBUTION OF CARBOHYDRATE IN VARIOUS TISSUES OF RAT, DOG, AND MAN

FIGURES REPRESENT RANGES FOUND ON A MIXED DIET

	Rat		*Dog*		*Man*	
	Glycogen %	Glucose Mg. %	Glycogen %	Glucose Mg. %	Glycogen %	Glucose Mg. %
Skeletal muscle	0.81–1.06	50–70	0.55	40–60	0.4–0.6	
Liver	2.5 –8.3		6.10		1.5–6.0	
Heart	0.3 –0.6		0.47			
Kidney			0.15		0.4	
Brain	0.08		0.1	57		
Skin	0.07	77	0.08	71	0.08	60–82
Blood and extra cellular fluids		90–129		60–80		60–90

Table 18 summarizes the distribution of the quantitatively important forms of carbohydrate in man and in certain laboratory animals. To some extent we must rely on the data from animals to interpret the relatively meager data available for human beings. This is because both glucose and glycogen (especially the latter) are labile substances when present in the tissues, and few opportunities present themselves to obtain human tissues under the proper conditions for accurate analysis. However, the close agreement of the reliable human data which we do have with that obtained from animals increases their significance.

THE FUEL OF MUSCULAR EXERCISES

In a very recent and exhaustive review of the subject, Gemmill[8] has aptly reviewed the situation as regards the fuel of muscular exercise as follows:

> From the survey of the literature it is obvious that the use of carbohydrate is of primary importance as a fuel for muscular exercise in man. The evidence comes from the slight increase in efficiency on a carbohydrate diet, the prolongation of muscular effort when carbohydrate is ingested, the fall in blood

sugar during long continued muscular exercise, and the production of lactate at the beginning of exercise and during severe exercise. The evidence that protein is used during exercise indicates that it is of secondary importance, probably to supply carbohydrate or carbohydrate intermediates. The results of experiments on fat utilization during muscular work have demonstrated that this substance is used indirectly. There is no experimental evidence at the present time for the direct utilization of fat by mammalian muscle. However, the indirect utilization of protein or fat must be an efficient process, since the exclusive feeding of these substances to man does not have a marked effect on muscular efficiency during short periods of exercise.

The significance of the above from the standpoint of nutrition is obvious. If carbohydrate is not available in foods, it must be made by the body from those materials which are in the diet in order to satisfy the fuel requirements of the active tissues. The eating of adequate amounts of carbohydrate therefore spares the body the work of making its fuel. This role of carbohydrate is naturally more important during moderate or severe muscular exertion than when the body is at rest. The great demand for fuel accompanying muscular exercise may rapidly exhaust the carbohydrate stores. This is evidenced by a decrease in glycogen content of the liver and muscles and, if the exertion is sufficiently severe and prolonged, may result in an abnormal lowering of the blood-sugar level. These phenomena are accompanied by increased breakdown of body protein (which is reflected in an increased excretion of nitrogen in the urine) and by an accelerated breakdown of body fat (as evidenced by a rise of the level of ketone bodies in blood and urine). When violent exercise is preceded or accompanied by a large intake of carbohydrate, the body works somewhat more efficiently, as judged by the calories expended per unit of oxygen intake. The increased nitrogen excretion and ketone formation are also minimized. The latter two effects of carbohydrate are examples of its protein-sparing and its antiketogenic actions.

THE EFFICIENCY OF CARBOHYDRATE AS A FUEL

It has been noted above that carbohydrate is a more efficient fuel for muscular exercise than are either protein or fat. This does not imply that portions of the protein or fat molecules are wasted when they are used. It does mean that the protein and fat molecules, when used as fuel, yield less than their total caloric value in the form which can be used by muscle. The remainder is used for the conversion of these molecules into suitable fuel. These conversions occur in the liver, which supplies the other organs with fuel by way of the blood stream.

Since the amount of glycogen present in the muscle at any one time is sufficient for only short periods of work, the carbohydrate used by the muscle must eventually come from the blood sugar. The glycogen within the muscle cells may be reasonably supposed to serve best in emergencies, when the muscle is unable to draw sugar from the blood as quickly as needed. But, as a matter of fact, glycogen is more than merely a conveniently packaged form of carbohydrate lying on the pantry shelf. It is now known that more energy is derivable from a certain amount of glycogen than from an equivalent amount of blood sugar. It requires a certain amount of energy to bring the blood sugar into the metabolic system of the muscle (as hexose-6-phosphate), and, therefore, all the energy inherent in the glucose is not available for useful work. On the other hand the breakdown of glycogen to the same stage does not require the addition of energy and hence makes all its inherent energy quickly available. This is not to say that one gets something for nothing from glycogen, for it required some energy to build up the glycogen in the first place. But this energy was expended during a quiescent period when plenty of it was available. The situation is analogous to that portrayed in Figure 11.[17]

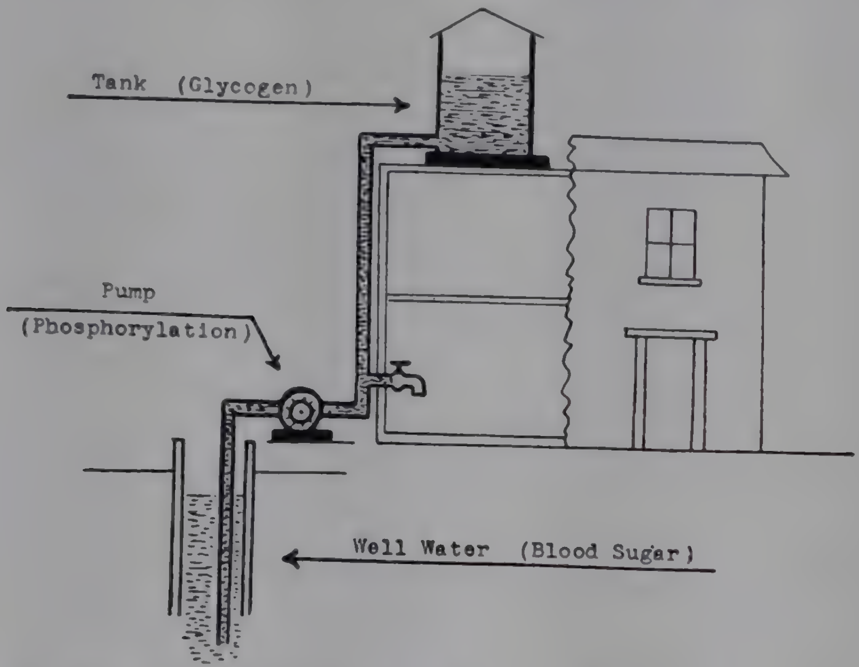


FIG. 11. A graphic representation of the significance of muscle glycogen, in which the water in the well represents the blood sugar, the pump represents the phosphorylating mechanisms, and the tank on the roof represents the store of glycogen.

Here the water in the well represents the blood sugar, the pump stands for the phosphorylating mechanisms, and the tank on the roof represents the glycogen store. It is readily understandable that when the tank contains stored water, the tap can deliver a rate of flow far beyond the rate-capacity of the pump. The water stored during periods when the tap is closed is at a higher level than the original source of the water and also stores some of the energy applied by the pump. This potential energy is released when the top is opened. Too great an outflow from the tap may, of course, exhaust the stored water and reduce the flow from the tap to the rate at which the pump is capable of operating. A similar situation may occur in muscle, when excessive rates of work over prolonged periods are attempted.

The application of these physiologic facts to clinical phenomena is exemplified by the greater stores of glycogen and of phosphate esters found in the muscles of animals which have been trained to perform prolonged work. This probably also applies to the physical abilities of manual laborers and of athletes. Conversely, the characteristically low muscle glycogen levels found in poorly controlled diabetic patients and in hyperthyroid individuals is accompanied by muscular weakness.

Special Functions of Carbohydrate

THE LIVER

Aside from its use as fuel in the liver, carbohydrate in this organ has protective and detoxifying actions and a regulating influence on protein and fat metabolism.

The liver of a well-fed normal animal contains a high percentage of glycogen as compared to any other tissue. It is known that such a liver is more resistant to various types of noxious agents than one which has been deprived of its glycogen by starvation or disease. This has been shown in animals for such various types of poisons as carbon tetrachloride, alcohol, or arsenic, and in humans for a variety of diseases accompanied by toxemias of bacterial origin. The defenses of the liver against toxic agents are of great importance to the body as a whole, for it is one of the chief functions of this organ to remove or destroy such toxins before they reach other vital tissues which are not equipped to deal with them. From this point of view, the maintenance of a high glycogen level in the liver is an essential for the health of the whole organism.

It is now known that most of the glycogen of the liver is present in the form of a complex with protein. It is a reasonable assumption that just as the protein part of the complex stabilizes the glycogen, so the glycogen would tend to protect the protein. More definite knowledge is available as regards the role of carbohydrate in specific chemical reactions which transform certain poisons into relatively innocuous substances. One such mechanism is the conjugation of glycuronic acid derived from carbohydrate with poisons which possess a phenolic hydroxyl group. Indeed this mechanism is one of the means by which the body regulates its steroid hormone metabolism, and protects itself from the harm which could result from an excess of the sex hormones.[9] It is also possible that the carcinogenic substances of the steroid type might be disposed of in the same manner. Another hepatic detoxifying mechanism is the acetylation of such substances as *p*-aminobenzoic acid and sulfanilamide.[11] In this type of conjugation the acetyl groups are derived from carbohydrate probably via pyruvate and acetyl phosphate. The rates of glycuronate formation and of acetylation have been shown to depend directly upon the concentration of carbohydrate in the liver.

The protein-sparing action of carbohydrate has already been mentioned. This action occurs chiefly in the liver, for it is this organ which is primarily responsible for the deamination of amino acids. Up to the point of deamination the fate of amino acids in metabolism is not finally determined. They may be used as building blocks from which to form proteins for the repair or growth of tissues, or they may be broken down for use as fuel. Once deamination has occurred the amino acids are permanently divorced from protein metabolism. The amino group is converted to urea and excreted, while the non-nitrogenous fraction is either used as a source of energy or is converted to carbohydrate or fat. The rate of deamination in the liver decreases as the available carbohydrate increases. An ample supply of carbohydrate thus conserves the products of protein breakdown in a form which may be used by the body to build or maintain its own protein structure. To put it in another way, a minimal intake of protein which may be adequate for the body's needs when taken together with good amounts of carbohydrate, may become inadequate when the carbohydrate intake is deficient.

The availability of carbohydrate to the liver also determines how much fat is broken down by this organ. There is no direct index of the rate of fat metabolism in the liver for, unlike protein, it is not accompanied by the excretion of a characteristic end product in the urine. However, it happens that fatty acids are not completely metabolized by the liver and that the end products of fatty acid metabolism in this organ are the so-called ketone bodies, β-hydroxybutyric and acetoacetic acids.[13, 19, 21] These ketone bodies must then go to the peripheral tissues for complete oxidation. Ordinarily the rate of breakdown of fat and of the formation of ketone bodies is such that the latter are promptly disposed of by the peripheral tissues, so that no significant amount appears in the blood or urine. But when fatty acid breakdown becomes excessively rapid and the rate of ketone formation in the liver begins to exceed the rate of disposal by the peripheral tissues, there begins to occur an accumulation of the ketone bodies in the blood and an excretion of these substances in the urine (ketosis). Under these circumstances in an otherwise normal animal, the administration of carbohydrate causes a prompt disappearance of the ketone bodies (antiketogenic action). This effect of carbohydrate occurs in the liver and is due to an inhibition of the breakdown of fatty acids. Together with the protein-sparing action of carbohydrate, its antiketogenic action serves to regulate the proportion of the different foodstuffs which are prepared by the liver for use as fuel by the peripheral tissues.

In discussing the special functions of carbohydrate in the liver, we have referred both to its glycogen content and to the "availability" of carbohydrate to this organ. These terms may or may not be synonymous, for it is still not known whether sugar may be used directly by the liver cells or must first be built up to glycogen. In any case the glycogen content of the liver is a good index of the amount of carbohydrate which is available to the hepatic cells; and from a nutritional standpoint it is important to remember that carbohydrate is the foodstuff which leads to the highest levels of liver glycogen. Fairly good glycogen stores in the liver can be obtained when protein is predominant in the diet, while a high fat diet results in a liver which is poor in glycogen. The medical uses of the high carbohydrate diet or of the intravenous administration of dextrose solution are directed towards the protection of the liver by insuring rich glycogen stores.[20] Protein has been used with the same ultimate purpose in mind, but it is less effective, probably in proportion to its convertibility to sugar.

There has been some work which purports to show that high-protein diets are as good or better than high-carbohydrate diets. There is good evidence that in certain specific types of poisoning, namely, those due to selenium and arsphenamine, protein is definitely superior to carbohydrate in protective value. Indeed, in the exceptional case of sodium cyanide poisoning, high-fat intake is better than either protein or carbohydrate. However, the evidence upon which the general superiority of protein is claimed is open to serious question. An examination of the data of Ravdin and his co-workers reveals that most of their comparisons were made between animals fed diets high in carbohydrate but inadequate in protein content and animals given very high-protein-low-carbohydrate diets. A fairer basis of comparison is, of course, adequate-protein-high-carbohydrate versus high-protein-low-carbohydrate. Table 19 summarizes such a comparison (made in the authors' laboratory) for carbon tetrachloride poisoning in rats. It may be seen that the adequate-protein-high-carbohydrate diet was definitely superior in lifesaving effect to both the high-fat diets and the high-protein diets. Chemical examination showed a correspondingly higher glycogen content of those poisoned animals which had been on the high carbohydrate diet.

It seems fair to conclude that, except in those instances where protein seems to exert a specific action, its value depends upon its glycogenic and lipotropic properties. Hence an adequate-protein-high-carbohydrate diet is generally applicable. In using such a diet, the increased requirements for the vitamins of the B complex should be satisfied. And in this connection it is important to note that large amounts of carbohydrate, together with a high dosage of thiamine, would tend to produce fatty livers unless counterbalanced by an adequate intake of choline or lipotropic amino acids.

TABLE 19. SUPERIORITY OF HIGH-CARBOHYDRATE-ADEQUATE-PROTEIN DIET IN THE TREATMENT OF CARBON TETRACHLORIDE POISONING*

			Liver (*All values in Gm. per cent*)		
Type of Diet	*No. of Rats*	*Survival* (Days)	Glycogen	Fat	Protein Nitrogen
High fat	12	12	0.58	10.86	2.50
High protein	12	17	1.67	5.68	2.34
High carbohydrate	12	28	2.27	6.06	2.66

* Mattar, E., and Taubenhaus, M. Unpublished experiments.

In attempting to drive the hepatic glycogen stores upward at a maximal rate for therapeutic purposes, physicians have often attempted to reinforce the effect of high carbohydrate intake by the simultaneous administration of insulin. This is not the place to discuss the physiologic action of this hormone, but it is important to note that the administration of insulin with carbohydrate to the *nondiabetic* organism actually results in a lower liver glycogen than if the same amount of carbohydrate had been given without insulin.[20] This is because insulin also influences the intake of glucose and the deposition of glycogen by the skeletal muscles. The much larger bulk of the muscles, as compared to the liver, serves to draw off most of the administered carbohydrate into the muscles and hence deprives the liver of glycogen which it might otherwise have deposited.

THE HEART

The previous discussion of carbohydrate as the most efficient fuel of muscular exercise and of the muscle glycogen as an important emergency source of contractile energy applies in even greater measure to cardiac muscle than it does to skeletal muscle. The latter can in some measure accommodate itself to a decreased supply of carbohydrate by decreasing its work. The heart cannot stop to rest. A temporary reduction in the supply of sugar to the normal heart (as in induced attacks of hypoglycemia) has little apparent effect on the organ, although a definite change in the electrocardiogram may be noted.[18] The apparent lack of influence of hypoglycemia on the heart may be due to the normally good glycogen stores to be found there. But in the heart which is damaged by disease and in which the initial glycogen stores are poor, hypoglycemia may precipitate stenocardial symptoms with angina and may even result in death. This has been noted for diabetic[18] as well as for nondiabetic cardiac patients, and in both it has also been observed that they may do better when the blood sugar is somewhat elevated even above the normal range. High carbohydrate therapy has been successfully used on this basis.

THE CENTRAL NERVOUS SYSTEM

Of all the organs and tissues in the body, the central nervous system is most dependent upon the minute-by-minute supply of glucose from the blood. In connection with the discussion on the fuel of muscular exercise, it was stated that carbohydrate was of primary importance, while protein and fat could be used only indirectly. As regards the central nervous system, it has been well established that only carbohydrate can be used.[14] The need of nerve tissue for glucose is even more specific than the previous statement would indicate. It is true, when slices of brain tissue are studied in vitro as regards their ability to maintain respiration at the expense of various substrates, that a number of degradation products of glucose will serve as well or better than glucose itself. However, none of these intermediates has been shown to have any ameliorating effect upon the hypoglycemic symptoms caused by lowering the blood level in vivo.[10] In other words, glucose as such has a specific influence and is indispensable for the maintenance of the functional integrity of the nerve tissue. When the blood sugar is lowered in a living organism, those tissues which have ample stores of glycogen may use the latter to tide them over the lean period. The nervous tissue has little glycogen, and it is doubtful whether the little which is present can be mobilized for use in emergencies. The glycogen content of nervous tissue remains more or less constant under most conditions, including hyperglycemia and hypoglycemia, and may be largely an integral part of the nerve structure. The unavailability of the glycogen present in the nerve cells for metabolic use is evidenced by the dramatically rapid development of hypoglycemic symptoms when the blood sugar is lowered.

The susceptibility of the central nervous system to hypoglycemic shock has been utilized recently in the treatment of schizophrenia and other nervous disorders. The hypoglycemia has been produced by the administration of large doses of insulin, and the earlier protagonists of the method spoke of the possible favorable effect of the hormone on the metabolism of the brain. It is now evident that insulin produces its results by lowering the blood-sugar level, as it forces the sugar into the peripheral tissues, largely the muscles. By this means the central nervous system is deprived of its indispensable substrate and suffers true shock or damage, which does not differ very much either in its mechanism or its results from the type of shock caused by asphyxia. Indeed the latter, in one form or another, has also been used as a method of treatment. That the insulin shock treatment is correctly named and is not due to a favorable influence on metabolism is also shown by the fact that prolonged hypoglycemia results in histologically demonstrable and functionally irreversible damage to brain tissue.[12]

The Transformation of Carbohydrate into Fat

In the previous discussion of fat as a fuel storage material, it was pointed out that when food in excess of caloric expenditure is ingested (whether in the form of carbohydrate, protein, or fat), the equivalent of the excess calories is deposited as fat in the adipose tissues. With this in mind it is, strictly speaking, incorrect to label any of the foodstuffs as being particularly "fattening." Any one of them can be so if taken in sufficient quantities. But, because of its proportion in the diet, its lower cost, and its use in confections, carbohydrate is quantitatively the most important precursor of fat.

The fat which arises from carbohydrate in the body is the so-called "hard" fat, composed in the main of the highly saturated palmitic and stearic acids. This is probably of more concern to stock raisers than to human nutritionists. The former have long known that they could control the physical qualities of the fat in meats by varying the proportion of carbohydrate and of oils in the diet of their animals. Of course, carbohydrate cannot completely substitute for fat in the diet since it does not carry with it the essential fatty acids and the fat-soluble vitamins which cannot be manufactured by the body.

The Interrelation of Carbohydrate and Protein Metabolism

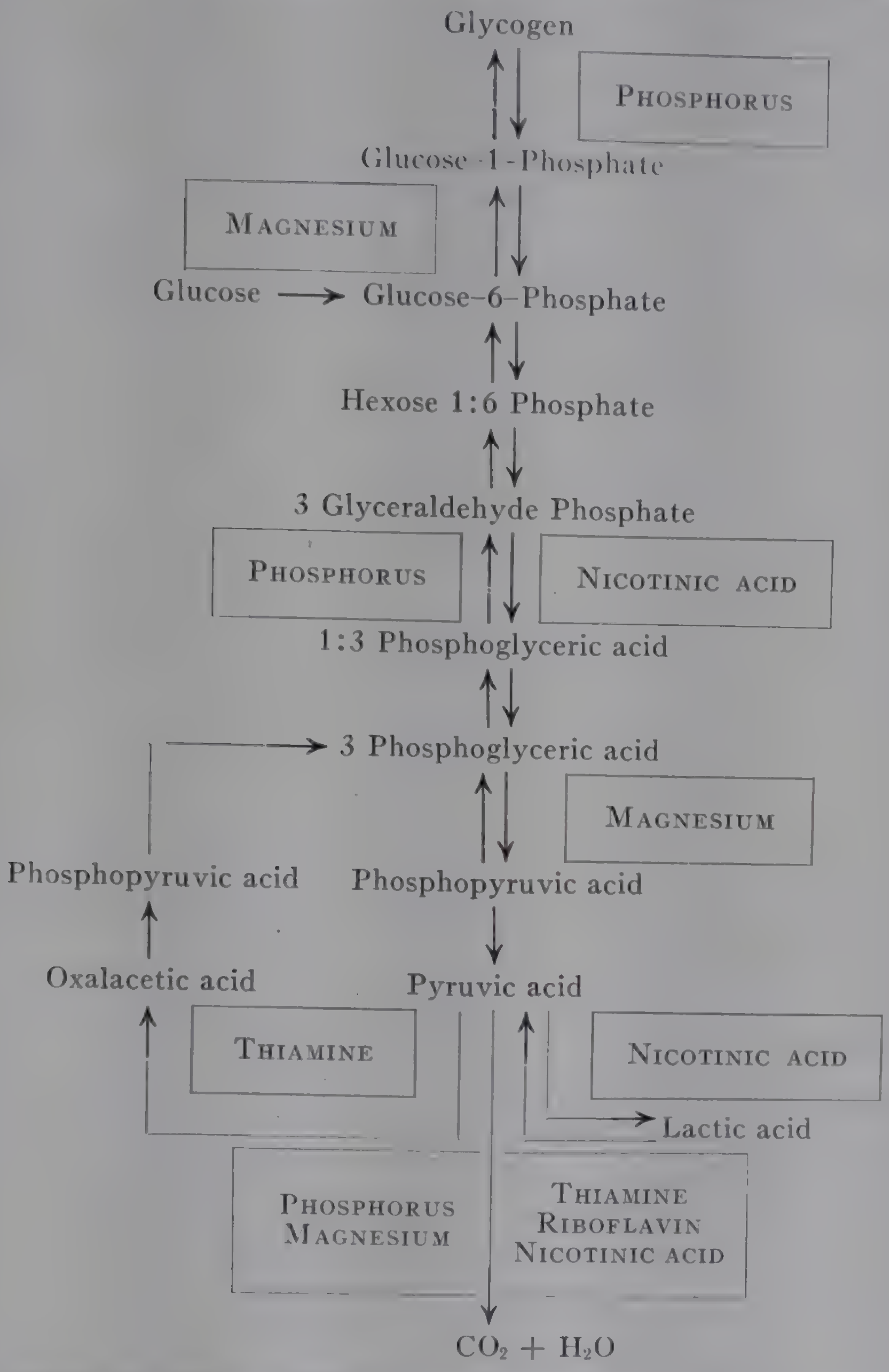
Earlier writers on metabolism have talked somewhat loosely of the formation of protein from carbohydrate. Strictly speaking, such a transformation is impossible because the amino groups which characterize the building stones of proteins must be derived from amino acids or proteins which are ingested as such. What can and does occur is that the amino group of an amino acid is exchanged with the keto group of a keto acid derived from carbohydrate, a process known as "transamination."[5] In this process the carbon residue of the amino acid reverts to a carbohydrate intermediate, so that there is not necessarily any quantitative increase in the amount of protein precursor resulting from the reaction. What the body gains from the interchange is the ability to transform one amino acid, which it may have in excess, to another which it may need.

THE IMPORTANCE OF THE VITAMIN B COMPLEX IN CARBOHYDRATE NUTRITION

It is now known that the vitamin B complex plays an integral part in carbohydrate metabolism and that part of the requirement for this group of vitamins depends upon the amount of carbohydrate which is eaten. Since this is so, why did not the knowledge of its existence arise much earlier, and why did not the race suffer from the lack of such knowledge? The answer lies in the fact that it is only in comparatively recent times that the natural union between the vitamin B complex and carbohydrate, which exists in whole grain and plants, has been broken by the industrial processing of foods. Before this occurred, the supply of the B vitamins was automatically adjusted to the amount of carbohydrate eaten, so that the occurrence of vitamin B deficiency with its consequent disturbance in nutrition is a comparatively recent development in the Western World. In the Orient, the earlier large-scale introduction of polished rice led to the first known instances of vitamin B deficiency (beriberi) and, indeed, to the first recognition of the existence of this group of vitamins.

The vitamins, as the name signifies, were first regarded as mysterious elements essential for life. As the different vitamins were successfully recognized and extracted in concentrated form from their natural sources, experimentation with these products led to the recognition of definite clinical syndromes resulting from their lack and cured, unless advanced to an irreversible stage, by their administration. More recently, the actual chemical identity of many of the vitamins has been established and a number of them have been synthesized. Coincidentally with the latter events, the development of tissue enzyme chemistry has revealed a great deal about the chemical steps through which the foodstuffs are broken down and used for energy. It is now known that each of the chemical steps is accomplished by the activity of one or more enzymes (protein catalysts) and that each of the enzymes requires one or more cofactors for its optimal activity. In some instances the cofactor is a simple mineral substance like iron or magnesium or phosphorus; in other cases the cofactor is a more complex organic substance, known as a coenzyme. Thus far, those vitamins whose functions are known have been found to be coenzymes or to give rise to coenzymes in the body.

Figure 12 outlines the known steps in the breakdown of carbohydrate and indicates the points at which the various components of the vitamin B complex play an essential role. The role of various minerals in carbohydrate metabolism is similarly indicated. It may be seen that definite knowledge is available about only three B factors, namely, thiamine, niacin, and riboflavin. It is to be expected that similar functions will eventually be found for the other factors in the B complex.



Glycogen
PHOSPHORUS
Glucose-1-Phosphate
MAGNESIUM
Glucose
Glucose–6–Phosphate
Hexose 1:6 Phosphate
3 Glyceraldehyde Phosphate
PHOSPHORUS
NICOTINIC ACID
1:3 Phosphoglyceric acid
3 Phosphoglyceric acid
MAGNESIUM
Phosphopyruvic acid
Phosphopyruvic acid
Oxalacetic acid
Pyruvic acid
THIAMINE
NICOTINIC ACID
Lactic acid
PHOSPHORUS
MAGNESIUM
THIAMINE
RIBOFLAVIN
NICOTINIC ACID
$CO_2 + H_2O$

FIG. 12. Points of action of vitamins and minerals in carbohydrate metabolism.

Since the breakdown of carbohydrate is essentially similar in all tissues and organs, it follows that a vitamin B deficiency will impair carbohydrate metabolism in every structure of the body. The clinical syndromes which have been described are, therefore, merely the most obvious manifestations occurring in tissues and organs which suffer most acutely and which are most easily accessible to examination. Consideration of Figure 12 also shows the fallacy of regarding any single factor of the B complex as more important than another, for the normal chain of events can be broken by a lack of any one of them. For this reason, and until we have isolated and know the precise function and optimal proportion of each component part of the B complex, a source containing all the factors remains the best protective dietary supplement with which to avoid the evils of modern food refinement.

The Utilization of Simple Sugars other than Glucose

In the previous section on the distribution of carbohydrate in the body, it was pointed out that all the hexoses absorbed from the gastrointestinal tract are converted into either glucose or glycogen. This conversion, which takes place largely in the liver, is ordinarily so efficient that there is little need to consider any other fate which sugars like fructose and galactose may undergo. However, under special circumstances, when the function of the liver is impaired or when these sugars enter the blood in overwhelming quantities, there occur interesting anomalies of carbohydrate nutrition which deserve some brief mention. Lactose is also of interest because of its formation in large quantities by the lactating breast of the female, at which time it may appear in blood and urine. The pentoses are sometimes involved in a hereditary anomaly of metabolism.

FRUCTOSE

The conversion of fructose to glucose occurs largely in the liver. When the hepatic mechanisms concerned with this conversion are impaired, either by liver disease or by an hereditary anomaly known as essential fructosuria, there is difficulty in disposing of the fructose taken in through the gastrointestinal tract, and it accumulates as such in the blood. Since it is a substance which is not held back by the kidney as efficiently as is glucose, it appears in the urine in abnormal quantities. Fructose is a reducing sugar which is not distinguished from glucose by the routine chemical tests. From the medical standpoint it is therefore important not to confuse fructosuria with diabetes mellitus.

LACTOSE AND GALACTOSE

Lactose is split into glucose and galactose in the process of digestion. It may, therefore, be considered together with the galactose which is ingested as such. However, the presence of lactose in milk and milk products renders it much more important than galactose from the nutritional standpoint.

In the previous discussion of the special functions of carbohydrate in the liver, mention was made of its protective and antiketogenic action. Liver glycogen, which is formed as a result of the intake of galactose or of lactose, may perhaps be more beneficial to the organism than glycogen which originates from other materials. This is because, for some unknown reason, the "galactose glycogen" is more stable. It has been shown that when galactose is administered to animals together with a ketogenic agent, the ketosis which follows is less than when glucose or fructose are similarly administered. Both lactose and galactose may be found in the blood and urine of lactating females. As with fructose, it is of importance medically to distinguish between galactosuria, lactosuria, and glucosuria.

PENTOSES

In contrast to the hexoses, which are important energy materials, the 5-carbon-atom sugars are much more important as part of the machinery of the body. Pentoses are incorporated in at least one vitamin (riboflavin), several tissue coenzymes (diphosphopyridine nucleotide, triphosphopyridine nucleotide, alloxazine adenine dinucleotide), and all the nucleoproteins. However, when pentoses as such are ingested they are not utilized but are eliminated, more or less quantitatively, in the urine and feces. It is possible that the pentoses which are eaten in combined form as part of natural food constituents (riboflavin and the nucleotides, for example) do contribute to the pentose content of the tissues. It is known that the body is able to synthesize pentoses for itself, from glucose by way of glycuronic acid. The hereditary anomaly known as "essential pentosuria" is as yet unexplained.

SUMMARY

We have seen that carbohydrate is not only the primary fuel of the body but is also involved in important portions of its functional machinery. The carbohydrate stores, though relatively small as compared to fat, play a protective role in some of the most vital organs. They may be of the utmost importance, when a rapid source of energy is required, to enable the organism as a whole to cope with an emergency in its environment. Despite all this, however, the evolutionary processes have resulted in so flexible a metabolic system that the higher mammals and man can get along very nicely when little or no carbohydrate is available. Under these circumstances the body makes its own carbohydrate fuel from noncarbohydrate materials. But this is a wasteful process because some energy must be used for the conversions, and there is more wear and tear of the metabolic machinery.

If, with the foregoing considerations in mind, we could divorce ourselves from previous dietary experience and were to attempt to construct an ideal adult diet, we would choose the following:

1. Protein sufficient in quantity and quality to repair the protein machinery from day to day and a little extra to be on the safe side. In the same category we would place a sufficiency of all the vitamins and minerals.
2. Enough fat to carry the essential fatty acids and fat-soluble vitamins and to make it unnecessary to eat too large a bulk of other food.
3. Carbohydrate sufficient to supply all the rest of the calories necessary to maintain weight.

The diet which has been outlined is a fair approximation of that which the human race has actually adopted on the basis of experience in those fortunate parts of the world where food resources are rich and the choice is not limited.

DISTURBANCES OF CARBOHYDRATE NUTRITION

The simplest nutritional disturbances with respect to a particular foodstuff are excessive and deficient intakes.

EXCESSIVE INTAKE OF CARBOHYDRATE

When the caloric intake is normal and the proportion of carbohydrate in the diet is excessive, two different kinds of malnutrition may result. The proportionate reduction in the amount of protein ingested may lead to a negative nitrogen balance, which may be accompanied by a deficiency of one or more of the essential amino acids. The unusual amount of carbohydrate eaten also increases the requirement for the vitamin B complex. Unless the intake of the latter is increased in parallel fashion by the proper selection of foods, a vitamin B deficiency may result even though the amount of the vitamin ingested would be adequate for a normal diet of equivalent caloric value.

When carbohydrate intake is excessive as part of general overeating, the result is obesity. The proportion as well as the amount of carbohydrate in the diet is apt to be high because of the relatively low cost of starches and sugars as compared to protein and fat and because of the development of unnatural appetites for cakes, pastries, candy, and other confections.

In many instances the basic problem of the obese patient is psychologic, requiring for its understanding the uncovering of the motives which led the patient to seek refuge in eating, and for its solution, the substitution of other satisfactions. But even after the basic urge to overeat has been suppressed, the patient still requires guidance as to the amount and kind of food to eat in order to lose weight satisfactorily and to reestablish a normal feeding habit.

The dietary treatment of obesity consists in a reduction of the total caloric intake to a level below that of the total caloric expenditure. Unfortunately, most obese individuals, who have taken years to accumulate their excess fat, want to remove it in a matter of weeks. This desire for speed should be resisted by the physician for, in general, the more slowly weight reduction is accomplished without discouragement of the patient, the better.* An average loss of one or two pounds per week should be considered as very satisfactory. This gives the body time to adjust to the new metabolic situation and the patient time to acquire a new and normal habit of eating.

Because of the role of excessive carbohydrate intake in the origin of obesity, there has been a tendency to over-restriction of carbohydrate in the treatment. It must be kept in mind that, on a subcaloric diet, the body does not restrict its utilization to the food ingested. If it did, no weight reduction would occur. The body makes up the caloric deficit by utilizing stored foodstuffs, which are largely fat. Hence the metabolic mixture which the body is actually utilizing, on a subcaloric regimen, is a high-fat mixture. It is therefore necessary to include enough carbohydrate in the diet to avoid the danger of ketosis (acidosis).

For the above reasons the anti-obesity diet should be moderately restricted as to calories (one-third to two-thirds of the normal requirement) and should be very low in fat content, adequate as to protein content, and relatively high in carbohydrate content, as follows:

1. *Fat:* 50-60 Gm. per day for an adult is about the minimum which permits a palatable diet, using ordinary meats as the chief source of complete proteins.
2. *Protein:* 1 Gm. per kilogram of "ideal" body weight per day avoids any possibility of protein deficiency. There is no harm in using more protein, providing there is no coincident increase in the fat intake.

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* For another discussion of obesity see Chapter 28, page 731, where much lower caloric intakes are prescribed. *(Editors.)*

3. *Carbohydrate:* The caloric equivalents of the fat and protein allowances are subtracted from the total calories prescribed, and the difference is given in the form of carbohydrate. This usually amounts to 75-150 Gm. per day, depending upon degree of caloric restriction.
4. *Vitamin supplements:* Food selection on a restricted diet is made much simpler if vitamin content is not a decisive factor.

DEFICIENT INTAKE OF CARBOHYDRATE

When the carbohydrate intake is low as part of a general reduction in the ingestion of all foodstuffs, the problem is that of undernutrition, in which the carbohydrate factor is of least importance. When the caloric intake is normal and the proportion of carbohydrate is very low, the chief danger is that of ketosis (acidosis) as outlined above. This danger is rather remote unless a large proportion of the calories is taken as fat.

ABSORPTIVE DISTURBANCES

In idiopathic steatorrhea (celiac disease, tropical and adult nontropical sprue, etc.) the absorption and sometimes the digestion of carbohydrates is interfered with. This group of disorders is characterized by dysfunction of the small intestine as evidenced by irregular motility and a sharp reduction in the rates of absorption of fats, fat-soluble vitamins, and carbohydrates. The unabsorbed carbohydrates undergo bacterial fermentation in the intestinal lumen, forming large amounts of carbon dioxide, and causing distention. The feces are bulky, fatty, sour, and frothy. The poor intestinal absorption of carbohydrates contributes to the loss of weight and strength, but it is not the important element in causing the main symptom complex. This is due primarily to the loss of certain essential nutrients: vitamins A, B, C, D, and K, calcium, and iron.

The oral glucose tolerance test, in celiac disease or sprue, yields a low and flat curve. That this is not due to a true disturbance in the regulation of the blood sugar level, of hepatic or endocrine origin, is shown by the fact that administration of glucose by the intravenous route yields normal tolerance curves.

It has been established, on an empirical basis, that certain articles of food which are high in carbohydrate content are well tolerated in the sprue-like syndromes. The best known examples are bananas and strawberries. In pediatric practice the banana diet has been successfully used to alleviate the diarrhea and to check the loss of body weight. More recently, diets high in protein and low in carbohydrate and fat have been used to advantage. These are supplemented by vitamins, calcium, and iron. The recent successful use of folic acid* is a most promising attack, since it may lead to a better understanding of the etiology of sprue.

Decreased absorption of carbohydrate from the gastrointestinal tract occurs in certain endocrine dysfunctions, but it is seldom of major consequence as compared to the other effects of the hormonal abnormality. The thyroid hormone has a direct influence on the rate of absorption of sugar, the latter being increased in hyperthyroidism and decreased in hypothyroidism. In Simmond's disease and in the later stages of anorexia nervosa, the depression of anterior pituitary function leads to atrophy of the thyroid gland. These conditions, as well as primary hypothyroidism, are therefore characterized by poor intestinal absorption of carbohydrate, which can be alleviated by treatment with thyroid gland preparations.

In Addison's disease there occurs a sharp fall in the sodium and chloride of the blood and extracellular fluids. This hypochloremia disturbs, among other things, the normal functioning of the gastrointestinal tract, affecting motility and the absorption of fats and carbohydrates. The correction of the abnormal mineral balance by treatment with salt and/or desoxycorticosterone restores the absorption of foodstuffs to the normal rate.

Patients suffering from depressed anterior pituitary or adrenal cortical functions are apt to develop hypoglycemia because: (1) there is a decrease in the ability of the liver to make glucose from noncarbohydrate precursors; and (2) the threshold of regulation of the blood sugar level is lowered, so that the glucose output of the liver is inhibited at lower blood-sugar levels. Hence, when sugars are ingested by such patients, the rise in the blood-sugar level (even though it is retarded by poor intestinal absorption) may be sufficient to inhibit the liver and cause a secondary drop in the blood sugar. The normal individual has a good regulatory mechanism which does not allow this blood-sugar drop to go too far below the range of normal. In hypopituitarism and in hypoadrenalism the drop is unchecked, and hypoglycemic symptoms may develop. It is therefore advisable in these conditions to restrict the amounts of free sugars in the diet and to provide carbohydrate in the form of less speedily absorbable foodstuffs, i.e., the starches of vegetables and cereals, instead of the sugars of fruits, pastries, desserts, and candy.

DIABETES MELLITUS[11]

The nutritional disturbance in diabetes is secondary to the metabolic disorder. There is no impairment of the digestion and absorption of carbohydrates; nor is there any qualitative difference in the utilization of the sugar which is carried by the blood to the body tissues. The pathologic physiology of diabetes primarily concerns the regulating mechanism which normally maintains a remarkably constant blood-sugar level—storing the excess carbohydrate absorbed during and after meals, and releasing it in a controlled manner between meals according to the demands of the active tissues. The liver, under the influence of the endocrine system, is the most important factor in this homeostatic mechanism. When preformed carbohydrate is not forthcoming from the gastrointestinal tract, the liver supplies the needs of the body by maintaining the constancy of the blood-sugar level with glucose which it produces from protein and fat.

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* See Chapter 21, page 543.

In diabetes there is an endocrine imbalance which renders the liver incapable of carrying on its blood-sugar–regulating activities. Sugar absorbed from the gastrointestinal tract is not gathered in by the liver, and the blood sugar rises to high levels. The hepatic production of sugar from protein and fat, which is normally inhibited by a rise in the blood sugar above the normal level, continues unchecked. The resulting persistent hyperglycemia leads to glycosuria, which represents a loss of calories as well as of water and minerals. In other words, the nutritional consequences of the uncontrolled diabetic state are a wastage of a certain proportion of the carbohydrate ingested and an uncontrolled and wasteful conversion of body protein and fat into unneeded carbohydrate; hence the loss of weight, dehydration, and demineralization, despite a large intake of food and drink. In addition, the excessive breakdown of fat by the liver results in the formation of large amounts of the ketone bodies, which lead to acidosis and coma.

The dietary treatment of diabetes consists essentially of reducing and systematizing the intake of carbohydrate so as to throw as little strain as possible on the impaired blood-sugar–regulating mechanism. Treatment with insulin more or less restores the regulating mechanism so that the accompanying diet need not differ from that of a normal individual in composition or amount. However, the injection of exogenus insulin under the skin one or more times a day cannot really duplicate the constant and responsive, secretory activity of the pancreatic islets. Hence, even under insulin treatment, the control of the hyperglycemia and glycosuria requires a certain regularity of food intake, both as regards the amount from day to day and the distribution during the day. But it is apparent that these dietary restrictions have no nutritional significance. They are merely a device to supplement our present inadequate methods of insulin administration.

It has been claimed that dietary supplements, particularly of the vitamin B complex, are of value in the treatment of diabetes. This must be strictly qualified. It is true that, like any individuals who cannot eat an unrestricted mixed diet, diabetic patients are apt to develop mild vitamin deficiencies. When they do, diabetic tolerance may be decreased and insulin requirement increased. Under these circumstances, the supplementation of the diet with vitamin B complex may result in a distinct improvement of the diabetes and permit a reduction of the insulin dosage. There is little or no evidence that a diabetic patient whose diet has contained adequate amounts of the B vitamins is benefited by the administration of additional amounts of the B complex.

RENAL GLYCOSURIA

This is an infrequent disorder in which the capacity of the kidneys to reabsorb glucose is impaired. Individuals suffering from this abnormality excrete glucose in the urine at normal or near normal blood-sugar levels.

The condition is not related to diabetes mellitus and the prognosis is excellent. In the majority of instances the glycosuria is negligible from the standpoint of the loss of calories, and no therapy is needed. Occasionally the loss of sugar in the urine is considerable and requires attention. The treatment consists of a diet high in protein and complex carbohydrates (cereals, etc.) and low in free sugars. On such a diet the blood sugar rise after meals is more gradual and moderate. The amount of glucose excreted is thereby reduced.

HYPERINSULINISM

This is a disorder caused by an excessive secretion of insulin from hypertrophic or adenomatous islets of Langerhans. The symptom complex is due to the lowering of the blood sugar level and the effect of this hypoglycemia upon the function and structure of the central nervous system. The manifestations are varied, depending upon the rapidity of blood sugar fall. Headaches, disorientation and personality changes, attacks of syncope or coma, convulsive fits, etc., may occur. The diagnosis is established first by finding a low blood sugar level in connection with the appearance of symptoms; and second, by the exclusion of other causes of hypoglycemia such as hypopituitarism, hypofunction of the adrenal cortex, or glycogen storage disease in children.

In the milder cases, the symptoms and signs may be precipitated most often one or two hours after meals as a result of the excitation of the excessive insulin secretion by the postprandial rise in the blood sugar level. Such cases may be successfully treated by dividing the daily food intake into frequent small meals, containing a high proportion of protein and the more slowly absorbable carbohydrates. The total caloric intake must, of course, be limited if the development of obesity is to be avoided.

In the more severe cases this may not suffice, and it is then necessary to resort to surgical exploration of the pancreas, with removal of the pancreatic adenoma if present, or resection of a portion of the hypertrophied gland.

LIVER DISEASE

Mild liver disease may render this organ unresponsive to its hormonal regulators and present a carbohydrate disturbance similar in appearance and effects to that of mild diabetes mellitus. The problem involved is chiefly diagnostic for, once the situation is understood, treatment with a high carbohydrate, adequate protein and low fat diet, including vitamin B complex supplements, usually leads to prompt hepatic recovery and a disappearance of the carbohydate disturbance. In severe liver disease, diagnosis is no problem, and the nutritional disturbance is of secondary importance in comparison to the other results of liver failure. Dietary treatment is similar to that outlined above.

Glycogen storage disease (von Gierke's) is a relatively rare condition in children, in which the liver, kidneys, and certain muscular organs store glycogen to excess because the enzyme system responsible for glycogen breakdown is defective. The increased size of these organs may cause certain mechanical and functional difficulties. Because the liver glycogen is not available for regulatory purposes, the blood sugar level tends to be low between meals regardless of carbohydrate intake. For the same reason, fat tends to be metabolized at an increased rate by the liver, leading to mild ketosis. No effective treatment for the underlying pathology is known.

BIBLIOGRAPHY

1. Althausen, T. L., Anderson, E., and Stockholm, M. Effect of adrenalectomy and of NaCl on intestinal absorption of dextrose. *Proc. Soc. Exper. Biol. & Med.* 40:342, 1939.
2. Althausen, T. L., and Wever, G. K. Galactose tolerance in hyperthyroidism. *J. Clin. Investigation* 16:257, 1937.
3. Bergmark, G. Untersuchungen über die Ausnutzung rektal und intravenös einjeführten Traubenzucker. *Skandinav. Arch. f. Physiol.* 32:354, 1915.
4. Bodansky, M. Introduction to Physiological Chemistry. New York, Wiley, 1934.
5. Cohen, P. P. "Transamination," in *Symposium on Respiratory Enzymes.* Madison, Univ. Wisconsin Press, 1942, p. 210.

6. Cori, C. F., Cori, G. T., and Goltz, H. L. Mechanism of glucose absorption from the intestinal tract. *Proc. Soc. Exper. Biol. & Med.* 26:433, 1929.
7. Follis, R. H., and Straight, W. M. The effect of a purified diet deficient in carbohydrate on the rat. *Bull. Johns Hopkins Hosp.* 72:39, 1943.
8. Gemmill, C. L. The fuel for muscular exercise. *Physiol. Rev.* 22:32, 1942.
9. Heller, C. G. Metabolism of the estrogens. *Endocrinology* 26:619, 1940.
10. Jensen, H. F. Insulin: Its Chemistry and Physiology. New York, Oxford U. Press, 1938.
11. Klein, J. R., and Harris, J. S. The acetylation of sulfanilamide in vitro. *J. Biol. Chem.* 124:613, 1938.
12. Lawrence, R. D., Meyer, A., and Nevin, S. The pathological changes in the brain in fatal hypoglycemia. *Quart. J. Med.* 11:181, 1942.
13. Mackay, E. M. The significance of ketosis. *J. Clin. Endocrinol.* 3:101, 1943.
14. Quastel, J. H. Respiration in the central nervous system. *Physiol. Rev.* 19:422, 1939.
15. Reder, R., and Gallup, W. D. The rate of digestion and absorption during avitaminosis B and G. *Proc. Oklahoma Acad. Sc.* 15:58, 1935.
16. Russell, J. A. The effect of thyroxin on the carbohydrate metabolism of hypophysectomized rats. *Am. J. Physiol.* 122:547, 1938.
17. Soskin, S. The storage and significance of tissue glycogen in health and disease. *Arch. Int. Med.* 71:219, 1943.
18. Soskin, S., Katz, L. N., and Frisch, R. The dual nature of the action of insulin upon the heart. *Ann. Int. Med.* 8:900, 1935.
19. Soskin, S., and Levine, R. Origin of ketone bodies from fats and their regulation. *Arch. Int. Med.* 68:674, 1941.
20. Soskin, S., and Levine, R. Carbohydrate Metabolism. Chicago, U. of Chicago Press, 1946.
21. Stadie, W. C. Fat metabolism in diabetes mellitus. *Ann. Int. Med.* 15:783, 1941.
22. Tolstoi, E. The effect of an exclusive meat diet on the chemical constituents of the blood. *J. Biol. Chem.* 83:753, 1929.
23. Yearbook of Agriculture, Food and Life. Washington, U. S. Govt. Printing Office, 1939, pp. 323 ff.

Chapter 9

CALORIC DEFICIENCY AND STARVATION

Ancel Keys

CALORIC malnutrition is historically the most important problem of nutrition. From present indications this seems likely to continue true, with undernutrition dominating all except a few favored areas where the balance tips and overnutrition threatens to be the more dangerous threat to health and longevity. Famine is customarily associated with crop failure, economic depression, and war. But undernutrition and starvation are not only produced by food shortage. Almost every major illness or injury produces a negative caloric balance and many chronic diseases regularly result in serious undernutrition (Chapter 1, page 22). In the absence of recognized disease, a great many people are habitually much underweight. The appetite is an amazingly accurate regulator but if it errs by only half a slice of bread and butter daily (90 calories), such a consistent error could mean a change of close to fifteen pounds of body weight in a year.* Ninety calories a day means 32,850 calories in a year, corresponding to about 3600 gm. of fat added to or taken away from the body. In general, the body weight changes about twice as much as the change in fat, so the total body weight change would be about 7.2 kg. or 15.9 lbs. These facts pertain to the person of normal weight and below; in the obese person, weight loss or gain may be almost pure fat.

Undernutrition affects every organ and function of the body and has a profound influence on personality and the emotional state as well. It undoubtedly affects the incidence and course of most diseases, but only diabetes mellitus and tuberculosis have received any real attention in this connection. Since it appears that many physiologic and biochemical characteristics are consistently and quantitatively altered by the state of caloric nutrition, it would seem that ultimate standards for the appraisal of health and disease should allow for this fact; for each functional characteristic of man the center and the extremes of "normality" are, theoretically at least, different for persons of varying degrees of emaciation and obesity. But knowledge is surprisingly defective on some basic subjects. Textbook discussions refer largely to fasting and acute starvation; the infinitely more common semistarvation has been little studied until recently, and habitual mild undernutrition has not really been studied at all.

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* For a more detailed discussion see pp. 721-724. (*Editors.*)

CALORIC REQUIREMENTS

Many tables of caloric "requirements" and "recommendations" have been devised. These are useful in dealing with large population groups and afford guidance in food production and distribution. They have practically no value in application to single individuals. The caloric requirement of the individual is that intake which will maintain his body weight at an optimal level while he engages in his customary or desired level of physical activity. In the period before growth is complete, the requirement must be modified to provide also the calories needed to maintain the optimal rate of growth; the latter is not necessarily the most rapid rate attainable.

So far, "optimal" body weight escapes precise definition. It is often confused with the so-called "normal average" weight given in "standard" height/weight tables, which is simply the average weight of persons of given height, age, and sex in a sample of the nondiseased population. According to insurance statistics on mortality, there is a considerable range, something greater than plus or minus 10 per cent of the mean, within which mortality is constant. At higher weights mortality rates are increasingly adverse. There are no precise data on the relation of body weight to total morbidity, to work productivity, or to social or personal adjustment. It may be that some degree of overweight is advantageous in one or more of these respects in spite of the disadvantage in longevity.

Overprecision in the use of height/weight tables must be avoided. Allowance should be made for body build or "frame" but there is no generally accepted system for evaluating this. A rough rule is to classify three types: Large, medium, and small frame, or heavy, medium, and slight build. In Appendix Tables E and F the values are given for these three body builds.

Functionally, the importance of caloric malnutrition would seem to be related to the proportion of fat to the active tissues of the body. A person with a small proportion of fat to other tissues is relatively undernourished, for example, while true obesity is the reverse regardless of actual body weight. In "healthy" young men about 12 per cent of the body weight is fat, on the average, and anything less than about 9 per cent seems to represent undernutrition. This "total fatness" may be estimated from the body density and, apparently, from the thickness of the skin folds. In young men, a skin-fold (double) thickness on the abdomen (midway between the umbilicus and the ischial process) of less than about 16 mm. (⅝″) suggests undernutrition.

In general, caloric requirements are related directly to body weight but are further dependent on age, sex, occupation, climate, and basal metabolism. A rough guide for sedentary adults (but not in bed rest) may be obtained in the following way. Calculate the twenty-four–hour basal metabolism according to age, sex, height, and *normal* (standard average) weight and multiply by one and a half. The result may be further corrected by adding 10 per cent for extremely cold climate and subtracting 10 per cent for hot climates. Since voluntary activity even in sedentary persons decreases with age, a final correction may be made by subtracting about 0.5 per cent for each year past the age of 35.

Whatever may be the result of such calculations or comparison with various tables for food intake, the final reference is the actual status of the individual. If the body weight is definitely low or if there is a progressive loss of weight, then the caloric intake is inadequate.

Individual Variability and Adaptations

Some of the bases for individual variability in caloric "requirements" have been noted above. The largest single factor is physical activity, but this is only partly accounted for in the energy expenditure in work in the regular occupation of the individual. In jobs characterized as "hard physical work" the energy expenditure off the job tends to be small, but in jobs demanding smaller physical effort the off the job activity has greater importance. On a forty-hour work week the free time beyond the needs of sleep, meals, and work is about fifty hours a week, and the energy expenditure in that time varies enormously in different individuals. Even on the job there are large individual differences in energy expenditure owing to variations in efficiency, in movement habitus, and in muscle tonus.

When the caloric intake is low, extraneous movements are suppressed, energy-saving postures are adopted, muscle tone is diminished, and the basal metabolism is decreased. Furthermore, as the body weight declines, the energy cost of movements is reduced in proportion. The result is a large measure of adaptation which automatically reduces the caloric deficit which would otherwise obtain. It is not possible to calculate the caloric deficit simply from the balance data for a normal state of nutrition. An inadequate diet which reduces the body weight by 10 per cent (from fairly normal weight) ordinarily reduces the energy expenditure by about 25 per cent unless there is a forced tempo of labor. At a body-weight reduction of 20 per cent (from a previously fairly normal weight) caloric balance is maintained on an intake of not much more than 50 per cent of the previous (normal) intake. Such considerations of the relation of weight loss and energy reduction explain why the rate of weight loss progressively decreases when a normal person chronically subsists on an inadequate diet and why life may be maintained for very long periods of time on a greatly reduced food intake.

The relative degree of obesity or emaciation from which a person starts on an inadequate diet naturally influences his rate of deterioration. Two men of the same age and height may differ by as much as 20 lbs. in total body fat even though they are both within 15 per cent of "normal" weight for height. But this fat difference represents some 80,000 calories and could, theoretically, compensate for a daily deficit of 500 calories for nearly six months. Actually, the resulting deterioration difference in two such men on the same inadequate diet is less marked than would be estimated on the basis of fat reserves alone because of the differential application of the adaptations noted above; the leaner man undergoes these adaptive changes at a faster rate and therefore decreases his expenditure of fat reserves more rapidly.

DEGREES OF UNDERNUTRITION

At present at least, the body weight is by far the best single guide in estimating the degree of undernutrition, but measurements of skin thickness are useful and the body density might be better if a simple method could be provided. The degree of underweight may be calculated from the present body weight and either the ideal weight for the height and age as given in Appendix Tables E and F, or the previous "normal" weight. If the latter is used allowance must be made for habitual obesity or leanness before the period of undernutrition began. The rate at which weight has been lost is important; the more rapid the weight loss the more serious is the problem.

The presence of edema complicates the situation. In severe emaciation, edema is the rule rather than the exception but it can be allowed for unless the edema is extreme. With Grades 3 and 4 edema, that is whenever edema extends well above the knees and there is fluid in the body cavities, the body weight becomes grossly unreliable as an indication of nutritional status. But such degrees of edema are very rarely the result of caloric starvation alone; their presence demands a search for other factors, including liver disease, sprue, infectious processes, severe anemia or hypoproteinemia, and cardiac failure. Grade 1 edema in emaciation (minimal pitting of the ankles and shins) seems to correspond to an excess of extracellular fluid amounting to 8 to 12 per cent of the gross body weight, and Grade 2 involves something like 10 to 15 per cent excess. These factors may be allowed for in the estimation of the true loss of tissue and of underweight, but it must be observed that in severe undernutrition without clinical edema there is almost always a relative excess of extracellular fluid; this becomes discernible only when it approaches 10 per cent of the body weight.

For the present purposes it seems better to ignore the ordinary abnormalities of hydration in undernutrition and refer to gross body weight; in cases of extreme edema or of clear dehydration, separate allowance must be made for the fluid abnormality, either by clinical impression or, better, from actual measurement of the extracellular (thiocyanate) fluid space. The following categories are made with these limitations in mind:

Slight undernutrition: weight loss to 10 per cent underweight. Unless very rapidly induced, this condition does not involve serious functional deterioration.

Moderate undernutrition: 10 to 20 per cent underweight. There is substantial change in many functions and characteristics, but the condition is often compatible with light or moderate work.

Severe undernutrition: 20 to 30 per cent underweight. There are profound changes in the majority of functions and characteristics. The patient can tend to his immediate personal wants and may even be able to do light work, but his condition is always at least potentially serious.

Extreme undernutrition: more than 30 per cent underweight. The patient is grossly abnormal and is rarely capable of any useful work.

The lethal limit for underweight is often stated to be a 40 per cent loss, that is body weight 60 per cent of normal, and this tends to be true in famine and in conditions where the patient is exposed to bad sanitation, insufficient shelter, and faulty care. But persons with still greater degrees of underweight occasionally survive. With good care it would be more accurate to place the lethal limit at about 50 per cent. There are records of recovery with even larger deviations from normal weight, especially in anorexia nervosa, but the lowest weights in these cases usually involve dehydration.

THE CAUSES OF UNDERNUTRITION

For the world as a whole, the vast majority of cases of undernutrition are caused simply by inability to obtain sufficient food, either because of crop failure or because of poverty. Such cases are relatively rare in the United States, but cases of severe undernutrition do occur among recluses and other isolated individuals, and slight to moderate caloric undernutrition may be found in any large community.

In the United States the greatest incidence of semistarvation is to be found in (1) persons with appetite failure from either psychic or physical reasons, (2) persons with impediments to food ingestion or digestion, and (3) persons with abnormal avenues of caloric loss. In the first category are such conditions as anorexia nervosa, Simmonds' disease (pituitary cachexia), tuberculosis, and many types of neoplasms. In the second category are cases of esophageal or pyloric stricture, severe gastritis, liver dysfunction, and so on. In the last category we may note conditions like sprue, ulcerative colitis, and uncontrolled diabetes. The increased energy expenditure in febrile states and in hyperthyroidism may result in undernutrition because the appetite does not assure compensation for the increased needs. Obviously, many diseases result in undernutrition from combinations of reduced appetite, impediments to digestion, and increased losses. All together, a large proportion of persons with serious prolonged illness become undernourished in the course of time. Indeed, local cellular undernutrition may well be the rule wherever there is tissue degeneration; the histologic picture in starvation is really rather characteristic of any degenerating tissue.

COMPLAINTS AND BEHAVIOR

Undernutrition produces characteristic complaints and behavior; where there are other abnormalities besides prolonged caloric deficiency these alter the picture, but usually in an understandable fashion. The following description refers to relatively uncomplicated severe undernutrition.

The starving man complains of weakness, easy fatigability, sensitivity to cold, constant hunger, dizziness on sudden movement, polyuria and nocturia, edema, depression, loss of ambition, impotence, and a sensation of being old. He complains if he has to stand and he objects to hard seats. Diarrhea is a major complaint among famine victims. There is often a "dry" bronchitis, but there are seldom any complaints of dyspnea, tachycardia, palpitation, or precordial pain. Headache occurs but it is not very prominent. Vision and hearing are not a cause for complaint except for occasional photophobia and intolerance to loud noises. The dominating sensations are almost always hunger, weakness, cold, and depression.

The most striking characteristics of the behavior are depression, apathy, and lethargy. The starved man lies or at least sits down if he can; if forced to stand he leans on anything available. In walking, the gait is slow and shuffling and he is prone to stumble over small objects. In speech he is slow and unemphatic; often the response to questions is long delayed. If the materials are available he is usually heavily clothed or bundled up. He is careless about his appearance and his manners and is indifferent to anything but food and his sorry state. Where there is appetite failure, the hunger and food interest do not obtain, but otherwise the picture is similar except for some cases of anorexia nervosa who exhibit considerable activity and a state of excitement.

Physical Appearance

The posture is drooping and the face is gaunt and sorrowful but otherwise devoid of expression (See XIII*b*, p. 105). The hair lacks lustre and appears unkempt and "staring." The eyes are dull and, on closer inspection, show sclerae resembling unglazed white porcelain; with the slit lamp the appearance is remarkably avascular. Emaciation is always marked unless there is much edema and even then the winged scapulae, deep suprasternal notch, prominent rib-cage, and pipestem arms reveal the extent of wasting.

The skin is pallid and grayish, sometimes with a yellow cast; in severe cases there are often irregular splotches of dirty brownish pigmentation (See XIII*d*, p. 105), particularly on the face about the eyes. The skin is cold, rough, and "dead" to the touch; when picked up between the fingers it is thin and inelastic as in the very aged. Ordinary gooseflesh is prominent in cool weather but many cases also exhibit areas of "permanent gooseflesh" (See I*a*, p. 57), especially on the extensor surfaces of the upper arms and legs; whether this is a true folliculosis or not is debatable. Slight cyanosis, accentuated in cold weather, is usually visible in the nail beds, less frequently also in the lips and over the malar prominences. The tongue is not characteristically abnormal except for dental impressions revealing lingual edema. The gums are pale and the interdental papillae are shrunken and retracted. The lips are frequently cracked and there may be thinning of the epithelium and maceration at the angles of the mouth, but true angular stomatitis and cheilosis are not characteristic.

The pulse is very slow and weak but regular. The heart sounds are faint and distant and the heart is not enlarged to percussion. Respiration is relatively slow and shallow. Except in very extreme states, exercise provokes only a fairly normal tachycardia which is not unduly prolonged in recovery, nor is there severe dyspnea. The tendon reflexes tend to be diminished and may be absent; other reflexes are usually not remarkable. Parasthesias are uncommon. Slight to moderate pitting edema (See XIII*d*, p. 105) is common; in the bed patient this may be discernible only as a puffiness about the eyes and a misshapen appearance of the face after lying on the side for a time. The urine is clear, pale, and dilute.

Tests and Measurements

The following figures apply to severe undernutrition. The body temperature is subnormal by 1° to 4° F. The blood pressure is low and the pulse pressure narrow. In basal rest the systolic blood pressure is usually below 100 mm. of mercury, most frequently between 75 and 95, and the pulse pressure is rarely as high as 30 mm. The basal metabolism is low, generally between –20 and –40 per cent using body surface standards. There is moderate anemia with a tendency to macrocytosis, the usual values for men being from 8 to 12 Gm. of hemoglobin per 100 cc. There is generally slight to moderate hypoproteinemia, the serum protein concentration commonly being between 5.0 and 6.5 Gm. per 100 cc., with only a trivial decline in ratio of albumin to globulin. The white blood count tends to be low, averaging from 3 to 5 thousand. The blood sugar is low but otherwise the blood chemistry is not remarkable.

Hearing and vision are not deteriorated when tested with standard measures; auditory acuity is frequently unusually good. Muscle strength is much diminished—30 to 50 per cent with the hand grip dynamometer—but muscle endurance is still more strikingly diminished. In exercise tests collapse comes quickly without excessive tachycardia or dyspnea. In women amenorrhea is universal. In men there is often impotence but if sperms are obtained few of them are motile and their viability is brief.

Common Complications

There are many complications which are often encountered in severely undernourished persons. Diarrhea is extremely common in famine, but it seems to be related to the use of coarse and indigestible foods and, possibly, to insanitary conditions; specific pathogens are rarely found in the feces, and intestinal antiseptics have little if any effect. In the Orient, caloric inadequacy is frequently superimposed on chronic protein and vitamin deficiencies, malaria, schistosomiasis, calcium deficiency, bacillary and amebic dysentery, trachoma, and a variety of skin diseases. The result is a high incidence of severe anemia and hypoproteinemia with consequent excessive edema, polyneuritis, paresthesias, visual disturbances (especially photophobia and night blindness), topical sores, and osteopathies.

Effects on Other Disease

Traditionally, famine is associated with pestilence, and it is widely held that undernutrition increases the susceptibility and decreases the resistance to infectious disease. In the case of tuberculosis this seems to be definitely true, even when allowance is made for the effects of the increased contacts, inadequate shelter, and defective hygiene often present in famine. In severely undernourished persons tuberculosis tends to run a fulminating course, although there may be little temperature elevation. Minimal lesions progress rapidly, with caseation, miliary spread, and invasion of glands and joints being far more frequent than usual. But for neither animals nor man is there good evidence for decreased resistance or increased susceptibility to infectious diseases in general.* Where reasonable sanitation and epidemic control is maintained, infectious diseases besides tuberculosis present no special difficulties. In food shortage areas differences in caloric nutritional state do not seem to be associated with major differences in the incidence or mortality of typhus, diphtheria, influenza, or septicemia. The percentage mortality of malaria and cholera may be increased because the critical stresses of these diseases are additive to stresses produced by undernutrition alone, but there are no real data available.

Severe undernutrition seems to be beneficial, if anything, in the so-called degenerative diseases. In diabetes mellitus both incidence and mortality are sharply decreased except in the juvenile form of the disease. In established cases of diabetes a period of food shortage or famine results in clinical improvement in most patients, insulin requirements are lowered, and complications are decreased. As the food shortage extends over a period of years the total diabetic picture in the community progressively improves.

A short period of famine—six months to a year or so—may not alter the incidence of cardiovascular disease, but the mortality declines and the clinical picture in hypertension and arteriosclerosis improves strikingly in many cases. Angina pectoris, coronary occlusion, and cerebrovascular accidents seem to diminish both in total number and in proportion to the number of patients with cardiovascular disorders. In animals, the incidence, rate of growth, and recurrence of tumors after surgery can be greatly reduced by prolonged extreme undernutrition, especially if this is begun before growth is complete. In man no such effects have been demonstrated, but cancer mortality in famine areas does not rise and may be somewhat reduced.

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* For a different conclusion see "Relation of Nutrition to Resistance to Infection" in Chapter 29, p. 748. (*Editors.*)

When reasonably good diets are reintroduced after severe undernutrition, there is evidence that the incidence of diabetes and hypertension increases beyond the normal (prestarvation) level. After the relief of the siege of Leningrad (1941–42) there was a veritable epidemic of hypertension, and somewhat similar findings have been reported in repatriated war prisoners and internees from the Orient.

TREATMENT

The total treatment in caloric undernutrition includes, besides caloric refeeding, correction of any other nutritional defects, elimination if possible of the causes of the undernutrition, general medical care, and measures aimed at full rehabilitation. The problems of refeeding depend on the degree of undernutrition, the presence or absence of appetite, the existence of other disease complications, and the character of the diet used before and during the period of starvation. In relief operations the most serious problems are apt to be the limited food supply available and the shortage of medical and nursing personnel, but the present discussion cannot touch on these questions.

In all cases refeeding should be started gradually and kept under control until the patient is approaching normal weight. In severely debilitated patients frequent small feedings of soft foods should be provided until there are clear but not necessarily very pronounced signs of improvement; usually it is only a matter of days until more ordinary foods in larger feedings can be given. In this early stage, milk, soft-boiled eggs, mashed potatoes, oatmeal, farina, cream soups, and ice cream are good. Excellent results are often achieved with only dried skim milk, sugar, and either farina or mashed potatoes.

Intravenous feeding is rarely necessary. In the extremely emaciated patient any intravenous fluid is dangerous and should be given only under constant surveillance, since pulmonary edema and sudden death can occur without warning. If the patient is unable or unwilling to cooperate, tube feeding may be used, but ordinary feeding should be introduced as soon as possible. In some totally uncooperative patients with anorexia nervosa, good results may be secured by using restraints and tube feeding for a week or two.

At an early stage it should be decided whether or not there are real signs of vitamin deficiencies. Bizarre neurologic or cutaneous manifestations as well as the more familiar signs of avitaminoses are reason enough to institute vitamin replenishment with selected foods or concentrates. Sources of all the vitamins are to be preferred to the pure chemicals because any vitamin deficiency which may exist is almost certainly mixed. Vitamin injections are rarely needed, but thiamine, niacin amide, or ascorbic acid may be so supplied if there are, respectively, indications of beriberi, pellagra, or scurvy.

Throughout rehabilitation the character of the diet should be good, but any diet that could be recommended for a school-age child will do well. There is no justification for using protein hydrolysates, fancy meat concentrates, or "predigested" foods. There seems to be no advantage to protein intakes greater than about 100 Gm. daily unless there are unusual avenues of nitrogen loss.* Normally, the correction of the anemia is slow, but iron intakes greater than 12 to 18 mg. daily do not accelerate the process.† There is no evidence that the healing of hunger osteopathies is really speeded up by large intakes of vitamin D and calcium. Similarly, there is no proof that hormone administration is beneficial in restoring sexual function.

The quantity of food is of much importance. While weight gain increases in direct proportion to the caloric intake, there are distinct limitations to the rate of recovery and restoration of the active tissues. There is a considerable tendency to the development of relative obesity (high ratio of fat to other tissues) and some danger of overloading the heart by a sudden large rise in metabolism. The goal should be to restore the body weight as rapidly as possible without getting into difficulties on either of the above accounts. For each 5 per cent of weight loss to be recovered, about a month of refeeding would be not far from optimal. In other words, if the patient is 30 per cent underweight, the refeeding program should provide that normal weight is regained in about six months. With more extreme degrees of emaciation an even slower rate of recovery may be better.

It is difficult to suggest actual caloric intakes to cover the wide variety of individual problems, but an example may be useful. Consider a man of average height, previously of fairly normal weight, who has lost 25 per cent of his body weight and has mild edema. Presuming that during refeeding he will engage in light to moderate work as rapidly as returning strength will allow, the following regimen (calories per day) might be satisfactory: First three days, 1500; next four days, 1800; second week, 2000; third week, 2300; fourth week, 2600; fifth week, 3000; sixth week and subsequent weeks until within a few pounds of normal weight, 3300. As the weight approaches normality the diet should be reduced. Salt intake should be restricted to a low normal level at all times, but water can be taken *ad lib.* The diet should be adjusted up or down if the weight curve is unsatisfactory. If edema recurs or if relative tachycardia develops, the diet should be curtailed and the patient should be restricted in activity.

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* Many would consider 100 Gm. of protein daily in the presence of protein depletion as a minimum, and larger amounts as desirable (see Chapter 7, p. 198). *(Editors.)*

† Iron deficiency anemias respond better to several times this amount of iron (see Chapter 11, p. 319). *(Editors.)*

A regular program of exercise is essential for full rehabilitation. Walking in the open air is excellent, but any mild to moderate exercise is useful. It is necessary to break habits of lethargy and to promote muscle rebuilding. Besides rehabilitation in terms of physical fitness, it is often necessary to consider psychologic rehabilitation. The general outlook and state of mind normally improve with refeeding, but it should be remembered that the patient has bad habits to break and that whatever may have been the cause of his undernutrition, it has almost always involved severe psychic trauma.

PROGNOSIS

Mortality in famine is highest in the aged and in small infants and, at all ages beyond a year or two, tends to be much higher in males than in females. Barring other complications, the prognosis for survival and recovery to a fairly normal state in persons from 5 to 50 years seems to be good up to weight losses (from normal average) of 25 to 30 per cent. Even weight losses of 30 to 40 per cent have a fair prognosis with reasonably good refeeding and medical care. But tolerance to severe undernutrition is progressively less in older persons. Serious signs are loss of appetite, relative tachycardia, delirium, and extreme dehydration or anasarca. The prognosis is very bad at degrees of 40 per cent or more underweight. Once definite improvement begins, the prognosis is good except for the ever-present dangers of tuberculosis, pneumonia, and, when the diet is unlimited, of heart failure.

Besides the prognosis for survival, the question of prognosis for full recovery is important. The evidence is defective in many respects but, on the whole, the residues from severe and even extreme undernutrition seem to be small. If there have been associated vitamin deficiencies, these may leave their marks, of course, and rare cases of hunger osteopathy may leave orthopedic deformities. But the general absence of persistent malfunction in the semistarved person who has been refed is remarkable.

Full recovery, however, is not quickly achieved. In young adults complete recovery from severe undernutrition cannot be expected in much less than a year; in older persons and with more extreme undernutrition, final rehabilitation may take considerably longer. In persons of middle age and beyond, in fact, there are no data to show whether or not full recovery is attainable. In young children, on the other hand, recovery from moderate undernutrition may be fairly rapid. Starvation only slightly depresses growth in length of children, although it may stop or reverse growth in weight. When such children are put back on to fairly good diets the growth deficits tend to be made up in a few years and the final body size tends to be substantially normal.

At all ages, psychic damage resulting from the complex of starvation and the associated events can produce lasting effects, but this sequel is rarer than might be expected. If anything, serious mental conflict tends to be reduced by unwilling starvation.

SELECTED BIBLIOGRAPHY

Within the extremely limited space provided for this subject it appeared impracticable to attempt individual documentation of the several points under discussion. From a very large available literature the following references are suggested as being most recent and informative.

GENERAL

Apfelbaum, E. (ed.) Maladie de Famine. Recherches cliniques sur la Famine executées dans le Ghetto de Varsovie en 1942. Warsaw, Am. Joint Distribution Committee, 1946.

Bigwood, E. J. (ed.) Enseignements de la Guerre 1939-1945 dans le Domaine de la Nutrition. Liège, Editions Desoer; Paris, Masson, 1947.

Brull, L., *et al.* Les Etats de carence en Belgique pendant l'Occupation Allemande 1940-1944. Liège, Editions Soledi; Paris, Hermann, 1945.

Hottinger, A., Gsell, O., Uehlinger, E., Salzmann, C., and Labhart, A. Hungerkrankheit, Hungerödem, Hungertuberkulose. Basel, Schwabe, 1948.

Keys, A. Caloric undernutrition and starvation, with notes on protein deficiency. *J.A.M.A.* 138:500, 1948.

Keys, A., Taylor, H. L., Mickelsen, O., Brözek, J., and Henschel, A. The Biology of Human Starvation. Minneapolis, Univ. Minnesota Press, in press.

Lamy, M., Lamotte, M., and Lamotte-Barrillon, S. La Denutrition, clinique, biologie, therapeutique. Paris, Doin, 1948.

Netherlands Red Cross Feeding Team. Report on Nutritional Survey in the Netherlands East Indies. The Hague, Netherlands Red Cross Society, 1948.

MORPHOLOGY

JACKSON, C. M. The Effects of Inanition and Malnutrition upon Growth and Structure. Philadelphia, Blakiston, 1925.

GENERAL BIOLOGY

MORGULIS, S. Fasting and Undernutrition. New York, Dutton, 1923.

FAMINE MORTALITY

DOLS, M. J. L., and VAN ARCKEN, D. J. A. M. Food supply and nutrition in the Netherlands during and immediately after World War II. *Milbank Mem. Fund Quart.* 24:319, 1946.

KERPEL-FRONIUS, E. Infantile mortality in Budapest in the year 1945. *J. Pediat.* 30:244, 1947.

VALAORIS, V. G. Some effects of famine on the population of Greece. *Milbank Mem. Fund Quart.* 24:215, 1946.

PRISON CAMPS

ADAMSON, J. D., TISDALE, P. K., BRERETON, D. C., and CARD, L. W. B. Residual disabilities in Hong Kong repatriates. *Canada. M. A. J.* 56:481, 1947.

BUTLER, A. M., RUFFIN, J. N., SNIFFEN, M. M., and WICKSON, M. E. The nutritional status of civilians rescued from Japanese prison camps. *New England J. Med.* 233:639, 1945.

CRAWFORD, J. N., and REID, J. A. G. Nutritional disease affecting Canadian troops held prisoner of war by the Japanese. *Canad. J. Research* E 25:53, 1947.

LEYTON, G. B. Effect of slow starvation. *Lancet* 2:73, 1946.

ZIMMER, R., WEILL, J., and DUBOIS, M. The nutritional situation in the camps of the unoccupied zone of France in 1941 and 1942 and its consequences. *New England J. Med.* 230:303, 1944.

ANOREXIA NERVOSA AND SIMMONDS' DISEASE

BERKMAN, J. M. Anorexia nervosa, anterior-pituitary insufficiency, Simmonds' cachexia, and Sheehan's disease. *Postgrad. Med.* 3:237, 1948.

BERKMAN, J. M., WEIR, J. F., and KEPLER, E. J. Clinical observations on starvation edema, serum protein and the effect of forced feeding in anoxia nervosa. *Gastroenterology* 9:357, 1947.

ESCAMILLA, R. F., and LISSER, H. Simmonds' disease: A clinical study with review of the literature; differentiation from anorexia nervosa by statistical analysis of 595 cases, 101 of which were proved pathologically. *J. Clin. Endocrin.* 2:65, 1943.

CARDIOVASCULAR SYSTEM

BRÖZEK, J., CHAPMAN, C. B., and KEYS, A. Drastic food restriction: Effect on cardiovascular dynamics in normotensive and hypertensive conditions. *J.A.M.A.* 137:1569, 1948.

HENSCHEL, A., MICKELSEN, O., TAYLOR, H. L., and KEYS, A. Plasma volume and thiocyanate space in famine edema and recovery. *Am. J. Physiol.* 150:170, 1947.

KEYS, A., HENSCHEL, A., and TAYLOR, H. L. The size and function of the human heart at rest in semi-starvation and in subsequent rehabilitation. *Am. J. Physiol.* 150:153, 1947.

SIMONSON, E., HENSCHEL, A., and KEYS, A. The electrocardiogram of man in semistarvation and subsequent rehabilitation. *Am. Heart J.* 35:584, 1948.

EDEMA

DENZ, F. A. Hunger oedema. *Quart. J. Med.* 16:1, 1947.

KEYS, A., TAYLOR, H. L., MICKELSEN, O., and HENSCHEL, A. Famine edema and the mechanism of its formation. *Science* 103:669, 1946.

SINCLAIR, H. M. Nutritional oedema. *Proc. Roy. Soc. Med.* 41:541, 1948.

TUBERCULOSIS

FABER, K. Tuberculosis and nutrition. *Acta Tuberc. Scandinav.* 12:287, 1938.

EMOTION AND PERSONALITY

FRANKLIN, J. C., SCHIELE, B. C., BRÖZEK, J., and KEYS, A. Observations on human behavior in experimental semistarvation and rehabilitation. *J. Clin. Psychol.* 4:28, 1948.

SCHIELE, B. C., and BRÖZEK, J. "Experimental neurosis" resulting from semistarvation in man. *Psychosom. Med.* 10:31, 1948.

NERVOUS SYSTEM

DENNY-BROWN, D. Neurological conditions resulting from prolonged and severe dietary restriction (case reports in prisoners-of-war and general review). *Medicine* 26:41, 1947.

SPILLANE, J. D. Nutritional Disorders of the Nervous System. Baltimore, Williams and Wilkins, 1947.

CALORIC REQUIREMENTS

FLEISCH, A. Ernährungsprobleme in Mangelzeiten. Basel, Schwabe, 1947.

KEYS, A. The calorie requirement of adult man. *Nutrition Abst. & Rev.*, in press, 1949.

ORR, J. B., and LEITCH, I. The determination of the calorie requirements of man. *Nutrition Abst. & Rev.* 7:509, 1937–38.

WOODBURY, R. M. Food Consumption and Dietary Surveys in the Americas. Montreal, International Labour Office, 1942.

YOUMANS, J. B., PATTON, E. W., and KERN, R. Surveys of the nutrition of populations. *Am. J. Public Health* 33:58, 1943.

Chapter 10

CALCIUM AND PHOSPHORUS MALNUTRITION

I. Snapper

In 1855, Trousseau,[38] the famous French clinician, described the syndrome of tetany and distinguished it from tetanus. Since then, our knowledge of the anomalies of the metabolism of calcium and phosphorus has grown considerably. The first description of the tiny parathyroid glands which regulate calcium and phosphorus metabolism was given by Sandström[30] in 1880. He found the two superior parathyroids; eleven years later they were rediscovered by Gley.[16] In 1895 Kohn,[19] after careful dissection, described that in man, in addition to the two glands described by Sandström, two inferior parathyroids were also present. Thirty years were to pass before parathyroid hormone was prepared from these little glands. This was accomplished in 1924 by Collip.[14]

In the meantime, the etiology of the clinical picture of rickets and osteomalacia had been elucidated. The pathologists gradually accepted Pommer's[28] idea that, anatomically, both diseases were the same. The curative action of cod liver oil had been known for centuries, although the active ingredient in it which actually cured the rachitic disease remained unknown. Following the discovery of the fat-soluble vitamins in 1922, the role of vitamin D in the metabolism of calcium and phosphorus began to emerge. In 1925, Mandl[23] of Vienna proved the importance of the parathyroids in the causation of skeletal disease. He removed a parathyroid adenoma in a patient with Recklinghausen's disease and obtained an almost miraculous clinical cure. Mandl also made note of the changes in the calcium metabolism before and after operation.

Albright and his associates,[3] after careful investigation, have emphasized the importance of parathyroid hyperfunction in the etiology of renal stones and certain gastrointestinal disturbances. Biochemical study of the serum and urine of patients with bone diseases now permits the differentiation of Recklinghausen's bone disease from many other diseases of the skeleton. It is now also possible to recognize hyperparathyroidism as the cause of many cases of nephrolithiasis and of rare cases of uremia and uncontrollable vomiting.

CHEMISTRY, PHYSIOLOGY, AND PATHOLOGY

All the calcium of the blood is present in the plasma and none is found in the erythrocytes. The normal calcium content of the serum varies between 9 and 11 mg. per 100 cc. About 50 per cent of the calcium in the serum is conjugated with protein, particularly with albumin. The remaining calcium is present in an ultrafiltrable form, or, in other words, it passes through a collodion membrane during filtration under pressure. This ultrafiltrable calcium is almost completely ionized and is present as calcium bicarbonate and calcium biphosphate. Only the diffusible part of the calcium in the serum is physiologically active.

The normal inorganic phosphorus content of the blood varies between 2.5 and 3.5 mg. per 100 c.c., and all of it is ultrafiltrable and ionized. It is important to know that the relationship between the ionized calcium, the carbon dioxide, the phosphate, and the acidity of the blood serum can be expressed in the formula

$$\frac{\mathrm{Ca} \times \mathrm{HCO_3} \times \mathrm{HPO_4}}{p\mathrm{H}} = \mathrm{K}$$

in which K is constant.

The formula indicates that if the carbon dioxide and the pH of the serum remain constant, the product of the calcium content (10-11 mg./100 cc.) and of the phosphate content (3-3.5 mg./100 cc.) of the serum must always be between 30 and 40. If, in tetany for instance, the calcium content of the serum drops to 6 mg. per 100 c.c., the inorganic phosphorus may be expected to rise to 5 or 6 mg. per 100 cc. In hyperparathyroidism the inorganic phosphorus often decreases to 2 mg. per 100 c.c.; thus the calcium must go up to 15 mg. In certain diseases this relationship does not hold true. In rickets, whether caused by insufficient intake of vitamin D or by fatty diarrhea, both the serum calcium and the serum inorganic phosphorus not infrequently drop to subnormal values.

Phosphatases, that is, enzymes capable of liberating inorganic phosphorus from organic phosphorus compounds, are of importance in calcium and phosphorus metabolism. These enzymes are instrumental in the formation of calcium phosphate which is deposited in the proteinic bone matrix during the process of bone formation. Alkaline phosphatase active at *p*H 9 is produced by the osteoblasts and the alkaline phosphatase content of the serum is an indicator of the activity of the osteoblasts. The alkaline phosphatase of the serum is expressed in units. The normal serum value is 3 to 4 Bodansky units or 10 King-Armstrong units per 100 cc.

An increase of the alkaline phosphatase of the serum is not specific for any bone disease because an increase of the osteoblastic function is found in Recklinghausen's bone disease, in Paget's disease, in rickets and osteomalacia, in malignant disease of the skeleton, and in many cases of polyostotic fibrous dysplasia. In myeloma, where the lesions are purely osteolytic and where no new bone formation takes place, the alkaline phosphatase content of the serum is practically always normal. For completeness it must be mentioned that in jaundice of the obstructive type the alkaline phosphatase of the serum is also increased.

A specific phosphatase, active at *p*H 5, is found in the prostate. This so-called acid phosphatase is of importance for the diagnosis of prostatic cancer. Whereas under normal circumstances the serum contains 2 to 3 Bodansky units of acid phosphatase per 100 cc., this value goes up rapidly as soon as the prostate carcinoma leads to metastases in the skeleton.

The calcium of the human body is stored in the skeleton, where it is present mainly in the form of calcium triphosphate and partly as calcium carbonate. The total calcium content of the body amounts to 1.5 to 2 per cent of the body weight, from 900 to 1500 Gm. being stored in the adult skeleton. The embryonic and fetal skeleton is built from calcium derived from the maternal skeleton. At birth the infant's skeleton contains about 45 Gm. of calcium. It follows that this must have been furnished by additional intake by the mother and/or depletion of her calcium stores.

During adult life there is a normal wear and tear of the bones, the bone absorption being caused by the activity of multinucleated osteoclasts. As a result of this wear and tear, several hundred milligrams of calcium are lost each day via stool and urine. To make up for this daily loss, calcium must be absorbed from the intestine. In food, calcium is present in both inorganic and organic form. The organic calcium compounds are hydrolyzed in the intestine and inorganic calcium is liberated and absorbed. The presence of vitamin D is essential for the absorption of calcium from the intestine. In avitaminosis D, little or no calcium is absorbed from the intestine; all the calcium is eliminated by way of the stool, and the urine is almost free of calcium. However, other factors may also inhibit calcium absorption from the intestine. In fatty diarrhea the stool contains large amounts of fatty acids which are conjugated with calcium and magnesium to form calcium and magnesium soaps. Fatty diarrhea must therefore lead to impaired calcium absorption. Another factor is the presence of excessive amounts of phosphates in the intestine which inhibits the absorption of calcium by the formation of insoluble calcium phosphates. This is the case in uremia, where mineral acids cannot be excreted by the diseased kidneys and large amounts of phosphates pass from the blood into the intestine. The phosphates conjugate with calcium, and in this way uremia leads to poor calcium absorption and to hypocalcemia. Occasionally, an excess of phosphorus in the intestine may be derived from special nutrients, especially from whole wheat bread, with resulting poor absorption of calcium from the intestine.

Under normal conditions and on a mixed diet, 0.4 to 0.8 Gm. of calcium is found in the stool and 0.15 to 0.3 Gm. in the urine per day. The calcium in the stool consists partly of the unabsorbed calcium of the food, but mainly of the calcium excreted by the intestinal wall. In many diseases, the relationship between urinary and fecal calcium becomes abnormal. Thus, in avitaminosis D little or no calcium is absorbed from the intestine, leading to an absence of calcium from the urine. The same holds true in fatty diarrhea. In other conditions, the calcium content of the urine is considerably increased, as for example in hyperparathyroidism, in certain decalcifying diseases of bone (carcinoma of the skeleton, multiple myeloma), and in the initial stage of osteoporosis. As practically all the calcium of the body is stored in the skeleton, bone changes result from most cases of calcium and phosphorus deficiencies.

For practical purposes, Albright[4, 7] has assumed that various forms of skeletal decalcification may be caused either by excessive bone resorption or by insufficient bone formation. Bone formation consists of deposition of calcium and phosphate in a proteinic osseous matrix, which has been laid down by the osteoblasts. Decalcification of bone may therefore result from the following conditions:

1. Inadequate activity of osteoblasts. This leads to decreased formation of proteinic bone matrix. If no matrix is present, calcium and phosphorus cannot be deposited, and the bone becomes decalcified. The decalcification resulting from insufficient formation of bone matrix is designated as *osteoporosis*. The several forms of osteoporosis are known as senile, postmenopausal, that due to Cushing's syndrome, and that due to immobilization.

2. Inadequate calcium absorption. Sufficient bone matrix may be produced, but the deposition of calcium and phosphorus in the matrix may

be impaired because insufficient quantities of calcium are absorbed from the intestine. Failure of the proteinic matrix to calcify results in *osteomalacia* and *rickets*. In these conditions, the bone trabeculae are surrounded by broad, noncalcified, osteoid zones.

3. Rapid increase of absorption of bone leads to a specific reaction of the skeleton, that is, to the development of *osteitis fibrosa*. In hyperparathyroidism or in chronic uremia, increased absorption of calcium phosphate from the bones is caused by the hyperactivity of the multinucleated osteoclasts. Concurrently, cellular bone marrow is replaced by fibrous tissue and the anatomic picture of osteitis fibrosa results.

PRIMARY CALCIUM AND PHOSPHORUS DEFICIENCIES

Primary calcium deficiency is extremely rare. The organism only needs to replace the calcium lost as a result of the daily wear and tear of the skeleton. This amounts to a few hundred milligrams per day, and there is scarcely a diet which does not contain this quantity of calcium. In general, therefore, calcium malnutrition is not the result of too small an intake of calcium. However, when the calcium-phosphorus balance is upset, the normal calcification of the skeleton is disturbed. It has been repeatedly noted that the calcium requirement increases when whole wheat bread is eaten. The bran in such bread contains considerable amounts of phytin, an organic phosphorus compound. The ingestion of whole wheat bread therefore leads to the presence of large amounts of phosphates in the intestine and to the formation of poorly soluble calcium phosphate. In order to guarantee the absorption of a sufficient amount of calcium, the intake of calcium must be proportionately increased as soon as whole wheat bread forms an important part of the daily diet.

The presence of large amounts of phosphorus-containing bran in the diet has only a limited practical significance for man. In horses on an exclusive bran diet, however, serious skeletal changes develop as a result of the excessive phosphorus intake. Such a diet was formerly common for horses used in mills, the bran being considered a valueless by-product. On a bran diet the calcium-phosphorus ratio falls below 1.5:1, whereas for normal skeletal development, the ratio must be higher than 2:1. Bran disease of horses is characterized by swellings in the region of the carpal and hock joints. The parts of the skull chiefly affected are the jaw bones and the zygomatic bones. The face grows large and misshapen, which explains the name of big head disease. The lower border of the mandible becomes cylindrical in shape, the teeth loosen and fall out. Deformities also occur in other bones, and fractures are common. By careful histologic investigation Theiler[36] proved that the bone changes are those of osteitis fibrosa. Some authors have reported that the alkali reserve of the blood of horses with bran disease is reduced, sometimes to one-third of the normal value. The urine becomes strongly acid in reaction and contains increased quantities of phosphates. If these data are correct, then the chronic acidosis from which these horses suffer may well be the cause of the osteitis fibrosa, as in human pathology.

Whereas bran disease is caused by excessive intake of phosphorus, skeletal lesions also occur in cattle with an insufficient intake of phosphorus. The grass and hay in many areas of the world are low in phosphorus. In these countries the calcium content of the serum of cattle is normal but the phosphorus content low. Evidently, to compensate for the insufficient phosphorus intake, the animals develop a craving for bone, or osteophagia. Such animals search for carcasses and consume the bones in order to get the much-needed phosphates. In South Africa, especially, cows are frequently encountered in the veldt crunching bones. It was well known that paralysis developed in aphosphorosis, and it was assumed that this paralysis was the result of skeleton changes. Theiler demonstrated that this paralysis is due to botulism caused by infection with *Clostridium botulinum*. This botulinus infection is secondary to the osteophagy; the animals, in order to obtain bones, ingest putrid carcass debris, teeming with botulinus bacilli. When the animals are fed bone meal or phosphates, the osteophagia is prevented and with it botulism. Such feeding also considerably improves the general condition of the animals, facilitates the growth of young animals, and increases the milk yield of cows.

CONDITIONED CALCIUM AND PHOSPHORUS DEFICIENCIES

The amount of calcium and phosphorus ingested may be normal, but bone lesions can result from an abnormal calcium and/or phosphorus metabolism. Such conditioned calcium and phosphorus deficiency gives rise to the following clinical syndromes: (1) Rickets and osteomalacia, in which insufficient calcium is absorbed from the intestine; (2) Osteoporosis, in which calcium and phosphorus are absorbed, but fail to be deposited in the skeleton; (3) Hyperparathyroidism, in which calcium and phosphorus are too rapidly removed from the skeleton; (4) Renal osteopathy, in which acidosis causes excessive calcium and phosphorus absorption from the bones. Here, at the same time, the resorption of calcium from the intestine is compromised by the excretion of large amounts of phosphates into the intestine.

1. RICKETS AND OSTEOMALACIA*

When there is insufficient absorption of calcium from the intestine, proteinic bone matrix is formed in the normal way but no calcium phosphate is available for deposition. As the normal wear and tear of the skeleton goes on and as the lost calcium is not replaced, decalcification gradually appears. Histologically, the result of insufficient calcium absorption from the intestine can be easily recognized by the presence of osteoid zones, that is, uncalcified zones of bone matrix surrounding the bone trabeculae.

Until recently, most authors defined osteomalacia and rickets as the reaction of the skeleton to avitaminosis D. Albright[4, 7] maintains that all conditions in which osteoid zones are found should be designated as rickets or osteomalacia, regardless of whether this histologic change is due to avitaminosis D or not. Thus, for Albright, avitaminosis D is only one of the causes of rickets and osteomalacia. In his opinion, renal tubular insufficiency and primary hypercalciuria may also act as etiologic factors in rickets and osteomalacia. In all these diseases, the proteinic matrix of the bone tissue is normal, but the deposition of calcium phosphate in the matrix is impaired and osteoid zones are developed around the bone trabeculae.

The reactions of the skeleton in rickets and osteomalacia are fundamentally identical. In both diseases the bone trabeculae are surrounded by broad osteoid seams and thus the definition of osteomalacia as adult rickets is certainly justified. The differences between the two conditions are not of fundamental importance and depend on the changes which occur at the cartilage-shaft junction of the bones during growth. In children and young individuals, in whom the epiphyseal disks are open and endochondral bone formation is actively going on, not only are osteoid zones found, but faulty calcification of the provisional calcification zones occurs as well. On the roentgenogram, the result of disturbed epiphyseal calcification is visualized as irregular and broad epiphyseal disks. By the time the patient has reached adulthood, the epiphyseal disks are ossified, and the main changes then obviously can only occur in the cortex of the bones.

Important clues to the identity of rickets and osteomalacia are the changes found in the latter disease in the costochondral junctions of the ribs. This is the only place in the adult organism where a cartilage-bone junction persists and it is here that the same proliferation of cartilage is found in the adult with osteomalacia as in the cartilage-shaft junctions in children with rickets.

* For discussion of rickets see Chapter 16, pp. 449-475.

Apart from the broad osteoid zones around the bone trabeculae in the long and flat bones, some decalcification is always present in both rickets and osteomalacia. In general, the decalcification is more extensive in osteomalacia than in rickets.

Rickets is designated as infantile rickets when it occurs in children below the age of 3 to 4 years and as late rickets when it occurs in children over 4 and in adolescents. In late rickets the same fundamental changes are found as in infantile rickets and in osteomalacia: the proliferating cartilage in the epiphyseal disks increases in size and the provisional calcification zone disappears. Osteoid seams and decalcification of the bone trabeculae, too, are present. The decalcification is usually more extensive than in infantile rickets, although perhaps less marked than in osteomalacia.

AVITAMINOSIS D AS THE CAUSE OF RICKETS AND OSTEOMALACIA

Disturbances of skeletal metabolism caused by the absence of vitamin D are usually the result of an insufficient exposure to sunlight. But avitaminosis D also occurs in fatty diarrhea (sprue, celiac disease, chronic jaundice, and chronic pancreatitis). In the latter conditions, insufficient absorption of fat-soluble vitamin D causes typical osteomalacic bone lesions, although the intake of vitamin D may be satisfactory. For the occasional cases of rickets in patients whose intake and absorption of vitamin D are apparently sufficient, the term "vitamin D resistant rickets" is used.

In the absence of a sufficient amount of vitamin D the absorption of calcium from the intestinal canal is reduced to a minimum, the fecal calcium excretion is increased, and the urinary calcium drops to traces. In the nontropical areas of the Orient, where avitaminosis D is frequent, the first sign of osteomalacia is often the absence of calcium from the urine of patients even if the serum calcium is still within the lower limits of normal, that is, between 9 and 9.5 mg. per 100 cc. In later stages, avitaminosis D leads to a decreased calcium content of the serum, accompanied by a normal phosphorus content, or to a normal calcemia with a decreased phosphorus content. The weakening of the bones due to impaired calcification causes an increased stimulation of the osteoblasts by the normal stresses and strains to which the skeleton is subjected, which leads to an increase in the alkaline phosphatase content of the serum. The diagnosis of avitaminosis D is proved when administration of vitamin D causes an improvement in the calcium absorption from the intestine, as shown by an increased calcium excretion in the urine and a decreased calcium content of the stool.

Administration of vitamin D to patients with avitaminosis D also increases the serum phosphate. Since the large amounts of calcium in the intestine occur mainly in the form of calcium phosphate, poor absorption of calcium, such as is present in avitaminosis D, must result in poor resorption of phosphate from the intestine. The reverse takes place when vitamin D is administered.

Normally, vitamin D is ingested with the food, especially in eggs, liver, butter, and milk, although winter milk and butter obtained from stabled cows contain only traces of vitamin D except when enriched by the addition of the vitamin. Apart from the amounts ingested with the food, the skin manufactures vitamin D during exposure to sunshine. Nowadays avitaminosis D is rare in adults in the Occident because practically everybody eats foods containing vitamin D. The modern popularity of sunbathing and sports is another important factor.

As an insufficient intake of vitamin D can produce not only early rickets, but also late rickets and osteomalacia, a study of the relation of these three affections in those countries where osteomalacia is prevalent provides much that is of interest. Osteomalacia is still endemic in northern India, in Japan, and in many of the northern provinces of China. There the diet contains little calcium, not very much phosphorus, and very little vitamin D. In China, milk and butter are unknown as dietary staples, and eggs, liver, and other animal products are eaten only by the well-to-do. Cereals are the main source of calories for the large majority of the North Chinese population. The cereals, for the most part millet, kaoliang, and corn, are eaten together with varying amounts of vegetables. The people who are somewhat better off use wheat flour and soybean flour and considerable amounts of fresh vegetables. Only the wealthier classes eat meat, fish, fowl, eggs, and liver. This means that the vitamin D intake of large numbers of the Chinese population is practically zero.

Obviously, a diet lacking in calcium and vitamin D must lead to a tendency to avitaminosis D. The urinary calcium content of ward patients in North China is often nil, even when the serum calcium level varies between 9.5 and 10 mg. per 100 cc.[34] Although latent signs of avitaminosis D are extremely frequent in Peiping, in most patients no clear-cut clinical signs of this disease can be discovered. In North China the unfavorable effect of the low calcium and vitamin D intakes is in most cases neutralized by the large amounts of sunshine. So long as the people work out of doors, a sufficient amount of vitamin D is produced in the skin and the signs of avitaminosis D are kept in check. But as soon as an individual is confined indoors, the opportunity is provided for signs of osteomalacia to develop. This explains why in North China the women are particularly prone to osteomalacia. The indoor life of the Chinese woman begins during puberty, for the Chinese girl is burdened with many household chores, and this at a time when the menstrual flow begins to withdraw a certain amount of calcium each month. After marriage, household duties keep the woman indoors even more, so that exposure to sunshine is reduced to a minimum. In addition, pregnancy and lactation constitute a serious drain on the calcium of the female skeleton.

In this connection, the observation of Miles and Feng[25] that the poorest women in Shansi, who work all day in the fields, do not suffer from osteomalacia, is very much to the point. In contrast, women who can afford to stay indoors all winter show the highest percentage of osteomalacia. Comparable conditions prevail in India, where osteomalacia and late rickets are particularly prevalent among the Mohammedan women for whom seclusion from public view also means insufficient exposure to sunlight. The same is true of the women of other religious sects who follow the same practice. In Kashmir, for example, the poorest women work on boats; although they live on the coarsest and poorest food, they never have osteomalacia, for they spend the greatest part of their lives out in the open. But among the better classes the rules of purdah are scrupulously observed; the women are secluded from the outer world and frequently suffer from osteomalacia.

Osteomalacia had become extremely rare in Western Europe by the end of the nineteenth and in the first decade of the twentieth centuries. But between 1917 and 1921, an endemic of osteomalacia occurred in Germany and Austria. The blockade of these countries by the Allies had reduced the supplies of milk, meat, fish, butter, eggs, and cheese to negligible quantities in both countries, and for two to three years most of these foodstuffs disappeared from the population's dietary. As a result, the calcium and vitamin D intake dropped sharply. The first patients with generalized decalcification of the bones appeared in the autumn of 1917; within a year their number had increased markedly, and by the spring of 1919 the epidemic of bone diseases had reached its climax. It then began to decrease rapidly, and only a few isolated cases appeared in 1921. During the Second World War, a similar endemic was observed in the occupied countries of Europe as the result of Germany's deliberate starving of the subjugated peoples. No cases were reported in Germany this time!

In general, hunger osteopathy shows the clinical picture of late rickets and osteomalacia. In the first epidemic, rapid improvement followed administration of cod liver oil, while vitamin D preparations were successful in the 1943–1945 epidemic. Tetany was a very frequent complication. In contrast to the experience in India and North China, the 1918 epidemic of late rickets and osteomalacia in Germany and Austria affected men more frequently than women, and the number of cases was greater in the cities and industrial centers than in rural districts. The explanation for that is that the boys who were too young for the battlefields were assigned to work in the war industries and were thereby deprived of exposure to sun. Women and girls, and the rural population in general, did not suffer this deprivation and so were less prone to attack by the bone disease. In the Second World War, on the other hand, mainly the women suffered from osteomalacia.

Not infrequently, avitaminosis D is superimposed upon some other disease.[35] This becomes possible when a patient with an unsatisfactory appetite is bedridden, at home or in a hospital ward. Under such circumstances administration of the vitamin will lead to a great improvement in the patient's symptoms and signs. It should be remembered, however, that only the superimposed avitaminosis is improved by the vitamin therapy, while the original disease continues unabated. This may be the explanation of the reports in the literature on the favorable effect of vitamin D therapy in so many different bone diseases.

ROENTGENOLOGIC PICTURE OF OSTEOMALACIA

At first, the bone changes caused by the disease can hardly be visualized on the roentgenogram. There may be a slight decalcification and a decreased number of secondary bone trabeculae, so that the structure of the spongiosa becomes more grossly reticular than usual. As the disease progresses the decalcification grows more extensive, and ultimately the bones of the pelvis, thorax, and extremities may become so decalcified that satisfactory roentgenograms can no longer be obtained.

The pelvis is characteristically deformed (see XII*f*, p. 101): there is an increased convexity of the sacrum and a marked narrowing of the outlet.[35] A deformation of the pelvis results which produces a so-called triradiate or wedge-shaped pelvis. Characteristic also is the coarse structure of bone, in evidence before excessive decalcification has set in. In such cases, although the skeleton still contains considerable amounts of calcium, the bones are already so soft that the acetabulum often intrudes into the pelvis. The pelvis becomes markedly asymmetric, the rims of the iliac bones are flattened, and symphysiolysis ultimately takes place. Bending and crumpling of the sacrum is a frequent occurrence.

In the extremities, the cortex is thin and separated into many layers—the so-called lamellation of the cortex. Later, incurvation of the bones and spontaneous fractures occur and the spongiosa or the cancellous part of the bone becomes strikingly rarefied.

A number of authors have in recent years insisted that transverse, small, ribbonlike, often symmetrical fissures, which Looser[21] called

Umbau Zonen (zones of transformation) are important for the diagnosis of osteomalacia. These fissures represent noncalcified callus and when found on the roentgenogram in grossly normal bone, are characteristic of osteomalacia. Thus, Albright[4, 7] considers the syndrome described by Milkman[26] consisting of "symmetrical fractures starting in the cortex" to be identical with osteomalacia. Similar horizontal broad fissures in the cortex also occur in other diseases, especially in Paget's disease. But contrary to the findings in osteomalacia, in Paget's disease the zones of fibrous callus occur in areas of bone showing definite pathologic changes. Dutch authors[29] who studied the osteomalacia which occurred in Holland during the German occupation also came to the conclusion that Milkman's syndrome must be due to osteomalacia.

Treatment: formerly, cod liver oil was the only effective agent for the treatment of osteomalacia and rickets. U.S.P. cod liver oil contains not less than 850 U.S.P. units of vitamin A and 85 U.S.P. units of vitamin D per gram. Most patients object to its taste and prefer other preparations. In the Far East, however, many people have no objection whatever to cod liver oil. As a rule, 1 teaspoonful, twice daily, is an adequate dosage. An oil easier to take is haliver oil, prepared from halibut livers, which contains not less than 60,000 U.S.P. units of vitamin A and 600 U.S.P. units of vitamin D per gram. The daily dose of haliver oil is 20 drops, or 4 to 6 capsules.

In later years synthetic preparations containing irradiated ergosterol have become popular. These may be given in the form of vitamin D capsules, containing 50,000 U.S.P. units, once or twice daily, or 5 to 10 drops of viosterol, not less than 210 U.S.P. units vitamin D per drop, thrice daily. Addition of calcium to the diet by way of milk and dairy products, or of calcium preparations such as calcium gluconate, 5 Gm. thrice daily, is helpful. It should be remembered that calcium ingestion without administration of vitamin D is valueless in rickets and osteomalacia.

Dangerous side effects may result from the administration of large amounts of vitamin D, especially if calcium is given at the same time. Hypercalcemia may appear and give rise to anorexia, vomiting, weakness, and ultimately to the formation of calcium precipitates in the kidneys, with consequent uremia. In rare cases this vitamin D intoxication has even been fatal. Fortunately, dangerous calcification of the renal parenchyma occurs only when the dosages of vitamin D are excessive (300,000–500,000 units daily) and are continued for a long time.

Exposure to sunshine and irradiation with ultraviolet light (quartz lamp) are often beneficial in the treatment of rickets and osteomalacia, and in severe cases of avitaminosis D, vitamin D therapy should be combined with ultraviolet light treatment.

RICKETS AND OSTEOMALACIA DUE TO STEATORRHEA

Insufficient intake of vitamin D is rare in the United States, and the main cause of rickets and osteomalacia is therefore absent. Such conditions occur here mainly in the rare cases of resistance to vitamin D and in steatorrhea due to celiac disease, sprue, chronic jaundice, or chronic pancreatitis.

On the basis of extensive experimental data, it seems certain that both generalized decalcification and hyperplasia of the parathyroids develop when bile is absent from the intestinal tract. But there are only scant observations of the development of skeletal changes in man under such circumstances.

When bile acids fail to reach the alimentary tract because of a complete biliary fistula or ligature of the common duct, large amounts of fats, fatty acids, and fat-soluble substances are excreted in the stool. In such cases, the fat-soluble vitamins, especially vitamin D, are lost in the feces, and the dangers of avitaminosis D become imminent. Furthermore, the fatty acids in the stool are present in the form of calcium soaps, whose presence also leads to loss of calcium salts from the body. It should be added that in the presence of a biliary fistula the daily loss of considerable quantities of alkali with the bile must result in acidosis; this is another cause of decalcification. In animals with an experimental biliary fistula, the first signs of bone softening appear within a few weeks, and spontaneous fractures of the ribs occur after sixteen weeks. Histologic evidence of osteitis fibrosa is found frequently. This decalcification can be prevented or cured by daily injections of vitamin D.

Buchbinder and Kern[11] found a generalized osteoporosis in animals after experimental ligature of the common duct. This skeletal disorder, too, can be explained on the basis of the absence of bile from the gastrointestinal tract and ensuing fatty stools.

Only a few cases of skeletal decalcification in man as a result of a longstanding biliary fistula or of chronic jaundice are reported in the literature. In such cases calcium and phosphorus of the serum are both low, with the alkaline phosphatase increased. All of the patients so reported have been old women, so that one cannot rule out the possible presence of senile, or even postmenopausal, osteoporosis. Our recent observation of a 48-year-old woman may therefore be of some interest here. The patient was still menstruating. In the course of a chronic obstructive jaundice caused by a stenosis of the common duct following an operation, a severe osteoporosis with vertebral compression developed. Vitamin D and calcium administration considerably lessened this patient's bone pains. The complete lack of effect of a series of testosterone propionate injections on the patient's complaints indicated that the decalcification did not have an endocrine origin.

The loss of calcium and of vitamin D in all cases of fatty diarrhea explains the frequent occurrence of rickets and osteomalacia in patients with Gee-Herter disease and sprue.

Treatment: if possible, the cause of the steatorrhea must be eliminated. Reconstructive surgery of the bile ducts is sometimes successful in relieving the jaundice. In sprue, a diet rich in proteins, especially lean and rare meat, is indicated together with intramuscular injections of crude liver extract, 5 cc. twice weekly. The steatorrhea caused by pancreatic insufficiency can sometimes be improved by diet and administration of pancreatic enzymes.

Apart from this causal treatment, ingestion of vitamin D and calcium, and exposure to sunlight or treatment with the quartz lamp, are indicated, as outlined for the treatment of avitaminosis D.

RICKETS AND OSTEOMALACIA NOT DUE TO AVITAMINOSIS D

Exceptional case reports have been published of patients with partial renal failure in whom at the same time multiple areas of calcification limited to the renal pyramids could be visualized in the roentgenograms. In this rare condition, known as lower nephron insufficiency with nephrocalcinosis, the body fluids undergo many biochemical changes. The chlorides of the serum increase and the carbon dioxide combining power of the serum decreases, but the pH of the urine remains normal. There is a hypercalciuria which has been considered to be an effort to compensate for the decreased ammonia formation resulting from the lower nephron insufficiency. The hypercalciuria is evidently the cause of the nephrocalcinosis. At the same time hyperphosphaturia is present. The inorganic phosphorus content of the serum is consequently decreased, and the calcium content is low or low normal. As a result of the increased calcium and phosphate excretion, no calcium is available for the formation of bone. The development of the bone matrix is normal, but no calcium phosphate is deposited, with the result that, at least in children and young individuals, broad osteoid zones form around the trabeculae—histologically characteristic of rickets and osteomalacia.

Albright[4, 7] has tried to explain why the bone lesions in lower nephron insufficiency differ from the renal osteopathy found in long-standing chronic uremia. In the latter condition, there is actual retention of acid radicals; this causes destruction of bone substance, with ensuing osteitis fibrosa. In lower nephron insufficiency, there is not enough acidosis to cause bone destruction; here the bone lesions develop because insufficient calcium is available for the normal deposition of calcium phosphate in the bone matrix.

The same reason for insufficient calcification of the bone matrix exists in the rare condition known as hypercalciuria without hypercalcemia.

Whether all three conditions—avitaminosis D, lower nephron insufficiency, and hypercalciuria—in which osteoid zones are found should be termed rickets and osteomalacia, or whether the designation should be reserved for avitaminosis D only, is purely a problem of semantics.

Treatment: in lower nephron insufficiency the biochemical disturbances and the subjective complaints are greatly improved by the administration of base in the form of daily doses of 12 Gm. of citric acid and 16 Gm. of sodium citrate dissolved in 200 cc. of water. The diet should be poor in sodium chloride but should contain additional calcium gluconate. Nevertheless, even when the general condition improves considerably under this treatment, the bone changes remain unaffected. According to Albright, improvement in the skeletal condition can be attained only by the combined administration of the alkaline mixture and vitamin D.

SUMMARY

Early rickets, late rickets, and osteomalacia are characterized by one histologic feature, namely, the presence of osteoid zones around the bone trabeculae. It is only the anatomic changes in the skeleton during the different phases of growth which are responsible for the more or less important modifications distinguishing the microscopic picture of the three diseases.

The broad osteoid zones are the expression of a lack of calcification of the normal proteinic bone matrix. By far the most common cause for this failure of calcium phosphate deposition is an insufficient intake of vitamin D. The decalcification leads to bone pains and deformations.

Insufficient dietary intake is responsible for the frequent occurrence of osteomalacia in certain of the nontropical areas of the Far East. In the West osteomalacia is a rare occurrence. It occurred, however, in endemic form during the two World Wars in the hunger-stricken countries.

Occasionally, osteomalacia is encountered in patients with long-standing jaundice or a biliary fistula, in sprue, in celiac disease, or in chronic pancreatitis. In these conditions, significant amounts of vitamin D and calcium are lost from the body via the fatty stools.

Osteoid zones also develop around the bone trabeculae in lower nephron insufficiency and in hypercalciuria without hypercalcemia. This is why certain authors consider the skeletal lesions in the latter condition to be those of rickets and osteomalacia.

The possibility that avitaminosis D is superimposed upon other diseases must be particularly considered in countries where the vitamin intake is low. Such an avitaminosis may occur when the patient becomes bedridden and is deprived of sunshine.

LABORATORY FINDINGS IN RICKETS AND OSTEOMALACIA

The following is found in avitaminosis D: (1) absence of calcium from the urine, the total amount of excreted calcium being present in the stool; (2) low value of calcium in the serum and normal phosphorus value, or low normal calcium value in the serum and decreased phosphorus value; increased alkaline phosphatase content of the serum.

Lower nephron insufficiency is characterized by: (1) increased urinary calcium; (2) in the serum, an increase in the chlorides, a moderate decrease of the calcium, and a marked decrease of the phosphorus; (3) low carbon-dioxide content of the serum, normal *p*H of the urine.

Treatment: administration of cod liver or halibut liver oil, or synthetic vitamin D preparations, together with exposure to sunshine or treatment with ultraviolet light (quartz lamp) is indicated in all forms of rickets and osteomalacia.

Lower nephron insufficiency must be treated with a diet poor in sodium chloride, to which a mixture of 12 Gm. of citric acid and 16 Gm. of sodium citrate is added each day. The bone lesions in this rare disease heal only when, along with the dietary treatment, vitamin D preparations are administered and exposure to sunlight is provided.

2. Osteoporosis

Osteoporosis, the result of a decreased formation of proteinic bone matrix, can be caused by any condition in which the synthesis of protein is impaired, for example in senility, in prolonged semistarvation, in the menopause, in Cushing's syndrome, and in prolonged immobilization.

In osteoporosis, the calcium which is resorbed from the intestine cannot be used for normal bone repair, because no bone matrix has been formed. In such cases the calcium is aimlessly carried about in the blood plasma and is excreted in the urine. Thus, in the initial stages of osteoporosis, hypercalciuria is a frequent occurrence, and renal stones develop in a considerable number of patients.

SENILE OSTEOPOROSIS

Senility is always accompanied by a decreased intensity of protein synthesis, as may be seen from the atrophy of skin, muscles, and other tissues rich in protein. The formation of proteinic bone matrix is compromised, and "senile osteoporosis" results.

With advancing old age, the cortex of the bones of the whole skeleton always shows signs of atrophy; the trabeculae of the cancellous bone become thinner and grow further apart; the greater part of the bone marrow becomes fatty, and only a few scattered islands of red bone marrow are in evidence. In extreme examples of the disease, the vertebrae collapse and the cortex of the other bones may become paper thin.

POSTMENOPAUSAL OSTEOPOROSIS

Investigation has shown that between the ages of 40 and 60 years osteoporosis occurs almost exclusively in women. Of Albright's[2] 42 patients with osteoporosis under the age of 65, 40 were women, and in all of them the menopause had set in or had been induced. Therein is the justification for assuming that the osteoporosis which develops in the 40- to 60-year age group may well be closely related to postmenopausal (endocrine) processes and can be differentiated from senile osteoporosis. In the former, the skull and extremities are practically always free from osteoporotic involvement, except in the most severe forms of the disease, and the lamina dura of the teeth remains normal.

The assumption that osteoporosis in women over 45 years of age is related to the postmenopausal syndrome is not based on statistical evidence alone. Experimental data also point to the influence of estrogenic hormones upon calcium metabolism. Estrogen administration to male and female pigeons leads to hypercalcemia and stimulates osteoblastic activity which results in increased bone density. It therefore seems reasonable to assume that a decreased production of estrogens during the menopause may result in decreased osteoblastic stimulation.

The clinical manifestations of the disease appear several years after the menopause, usually preceded by a prodromal period of fatigue and fleeting pains. A slow but marked loss of stature is frequent. Sharp pain in the back often develops after a minor accident or a severe jolt, and roentgenographic examination of the spine then reveals marked decalcification localized especially in the dorsal and lumbar portions. The bone atrophy is often so advanced that only the end plates of the vertebrae are denser than the intervertebral disks. In the dorsal area of the vertebral column, the pressure is transmitted mostly to the anterior parts of the vertebrae. In the lumbar area, the pressure is greatest in the center of the vertebrae; here, therefore, the osteoporosis causes the formation of fish or hourglass vertebrae. The elastic intervertebral disks expand, at the expense of the softened vertebrae, and often become wider than the vertebrae themselves. Ultimately, a complete collapse of one or more vertebrae may occur. In less advanced cases, evidence is found of herniation of the nucleus pulposus (Schmorl's nodules), the most elastic part of the intervertebral disk.

It is of practical importance that administration of male hormone, and occasionally also of estrogen, leads to great clinical improvement in a considerable number of patients with postmenopausal osteoporosis. The effect of male hormone in this condition may be ascribed to its metabolic action. Administration of this hormone increases nitrogen retention considerably and stimulates tissue growth by formation of new protein. Concomitantly, the phosphorus, potassium, and calcium balances become positive. In postmenopausal osteoporosis, a condition in which insufficient proteinic bone matrix is deposited, stimulation of protein production may well lead to increased deposition of protein matrix, after which the bone can begin to recalcify.

Although it must be stressed that patients with postmenopausal osteoporosis often show remarkable improvement after administration of testosterone propionate, it should be added that, actually, recalcification of the osteoporotic bones is only rarely observed in such cases. The pains often disappear and not infrequently, with the help of an orthopedic corset, the patient can be mobilized after a series of injections. But even in patients in whom the clinical improvement is highly satisfactory, recalcification of bone can hardly ever be visualized on the roentgenogram.

Treatment: testosterone propionate, in doses of 25 mg., can be given intramuscularly. In moderately severe cases, 3 such injections per week, which are usually tolerated without disagreeable side effects, are required. In severe cases, 6 weekly injections are necessary. A certain amount of hoarseness, sometimes a slight hirsutism, occasionally acne and excessive vaginal secretion are noted by patients receiving testosterone therapy. These disagreeable side effects can often be neutralized by simultaneous biweekly administration of estrogens.

OSTEOPOROSIS IN CUSHING'S SYNDROME

Hyperfunction of the adrenal cortex may give rise to different syndromes. If adrenocortical hyperfunction is present at birth, the infant will show the signs of pseudohermaphroditism. In children or adolescents, adrenocortical hyperfunction leads to precocious development. In adults, this condition often produces an adrenogenital syndrome, that is, masculinization in women, feminization in men. In such cases, large amounts of 17-ketosteroid substances are excreted in the urine, and the sexual changes are in the foreground while the metabolic abnormalities are less striking.

There are other cases of adrenocortical hyperfunction in adults in which the reverse takes place. In these patients, remarkable metabolic abnormalities develop while the change in the patient's sexual characteristics is less outstanding. The latter syndrome, known as Cushing's syndrome, most frequently occurs in women, sometimes in children, and with relative rarity in adult men. It is characterized by obesity of face and neck (moon face), mild hirsutism (without enlargement of the clitoris or deepening of the voice), impotence in men, amenorrhea in women, mild polycythemia, hypertension and early arteriosclerosis, diabetes which is usually mild but resistant to insulin, large reddish or purplish striae on abdomen and thighs, asthenia, weakness, and osteoporosis, usually of the spine. In contrast to the cases of so-called adrenogenital syndrome, the 17-ketosteroid excretion in Cushing's syndrome is normal or only slightly elevated.

Cushing's syndrome may result from cancer or adenoma of the adrenal cortex and also from unilateral or bilateral hyperplasia of the adrenal cortex. A basophilic adenoma of the pituitary gland may give rise to comparable signs and symptoms, but in such cases the pituitary lesion is probably always accompanied by a hyperplasia of the adrenal cortices.

It is certain that in Cushing's syndrome the metabolism is abnormal in many respects, the error in protein metabolism being the most important. This results in an inadequate repair of tissue, as shown by the atrophy of the muscular system. It is Albright's[2, 7] opinion that the impairment of protein metabolism in Cushing's syndrome leads to an insufficient formation of bone matrix and thereby to osteoporosis, mainly involving the spine, pelvis, and ribs. The vertebrae grow less radiopaque, and the terminal plates of the vertebrae stand out on the roentgenograms. The intervertebral disks compress the bony part of the spine and fish or hourglass vertebrae develop in the lumbar portion, while wedging of vertebrae is prominent in the dorsal portion. In the later stages of the disease, actual compression fractures of the spine occur. Sussman and Copleman[36] have drawn attention to the expansion of the ribs to about twice their normal diameter just proximal to the costochondral junctions. This anomaly, which they have frequently found in Cushing's syndrome, has not been observed in postmenopausal osteoporosis. In more advanced cases, the skull and the long bones also become osteoporotic. In the calvarium, the decalcification is localized mainly in the frontal and parietal bones. Triangular or ameboid-shaped zones of decalcification with ill-defined margins may at times be seen. The greatest proportion of patients with Cushing's syndrome show definite osteoporosis.

Although the impairment of protein synthesis has been emphasized as the most important cause of the several forms of osteoporosis, this hypothesis fails to clarify all the characteristics of the osteoporosis in the menopause and in Cushing's syndrome. If these two forms of osteoporosis were due only to a changed protein metabolism, why then is the postmenopausal osteoporosis limited to the spine and pelvis, only rarely attacking the skull, whereas in Cushing's syndrome the skull is commonly involved and the rest of the skeleton frequently decalcified? Thus the hypothesis fails completely to explain the localization of the skeletal decalcification—one of the most characteristic clinical features of postmenopausal osteoporosis. Furthermore, if the osteoblasts are paralyzed in the various forms of osteoporosis, it is difficult to explain the luxuriant callus of the rib fractures in Cushing's syndrome.

Treatment: as in postmenopausal osteoporosis, improvement of the protein metabolism by the administration of testosterone propionate may halt the progress of the osteoporosis in Cushing's syndrome. Sometimes, the pains disappear and new fractures no longer occur, but even in patients who show remarkable clinical improvement, actual recalcification of the skeleton is hardly ever discovered on serial roentgenograms.

OSTEOPOROSIS DUE TO IMMOBILIZATION

The stresses and strains to which the skeleton of an active individual is subjected form the normal stimuli for osteoblastic activity. Immobilization must therefore lead to impaired function of the osteoblasts, that is, to decreased formation of proteinic bone matrix. The more complete the immobilization, the more extensive the inhibition of the osteoblasts, the less proteinic matrix is deposited, and the more severe the ensuing osteoporosis. Thus, the immobilization of a limb in a plaster cast leads to atrophy of the immobilized part of the skeleton. If a large part of the skeleton is encased in plaster, acute osteoporosis can give rise to dangerous side effects. This is especially true when the patient ingests large amounts of milk and other calcium-rich food, and when at the same time vitamin D is administered in order to accelerate the bone healing. Under such conditions, excessive amounts of calcium are absorbed; these, however, cannot be used for bone formation, because no proteinic matrix is being formed. Hypercalcemia and hypercalciuria then result, and renal stones form frequently. In view of the large consumption of milk in the United States, it is not surprising that renal stones developed in 7 per cent of the American soldiers who suffered a fracture of the femur. Even more frequent is the development of renal stones in patients with fractures of the pelvis. Such stone formation, however, is infrequent in patients with fractures of the upper extremity, for in such cases a much smaller part of the body is immobilized.

A renal shutdown sometimes occurs during such immobilization, as a result of precipitation in the renal parenchyma of the excessive amounts of calcium which float around aimlessly in the blood plasma and which ultimately must be excreted. Renal shutdown is a dangerous, occasionally a fatal, complication. In such patients the high calcium content of the serum and urine may give the impression of hyperparathyroidism. It is exceedingly important to differentiate between the hypercalcemia due to hyperparathyroidism and that due to immobilization. In the latter instance no hypophosphatemia is found and removal of the plaster cast and mobilization of the patient may be a life-saving measure.

SUMMARY

When osteoporosis occurs in individuals between the ages of 40 and 60 years, it does so almost exclusively in women after natural or artificial menopause has set in. Postmenopausal osteoporosis is closely related to the altered protein metabolism which is inherent to the menopause. The same mechanism is the cause of osteoporosis in Cushing's syndrome. In both forms of osteoporosis, considerable improvement can be obtained by treatment with testosterone propionate, which stimulates the synthesis of proteins and thereby the deposition of bone matrix. In some cases the male hormone administration can be supplemented with estrogens.

Osteoporosis due to immobilization in plaster casts is of great clinical importance. This form of the disease often leads to formation of renal stones. When hypercalcemia and hypercalciuria during immobilization result in a renal shutdown, immediate mobilization of the patient, despite the fracture, is essential in order to prevent a fatal outcome.

LABORATORY FINDINGS IN OSTEOPOROSIS

Since the condition is due to impaired deposition of bone matrix, a tissue consisting mainly of protein, its primary cause is not a disturbance of inorganic metabolism. The calcium, inorganic phosphorus, and alkaline phosphatase values of the serum usually remain normal, although in the initial stages of the disease hypercalcemia and hypercalciuria may be found. The latter is constantly observed in osteoporosis due to immobilization.

3. Hyperparathyroidism

The problem of parathyroid function entered a new phase in 1926, when Mandl[23] reported that remarkable improvement in the symptoms and signs of generalized fibrocystic osteitis or Recklinghausen's bone disease had followed removal of a parathyroid adenoma. This operation has since been performed successfully on hundreds of patients with Recklinghausen's disease. It has gradually become evident that the disturbance of the calcium and phosphorus metabolism resulting from parathyroid hyperfunction plays an all-important role not only in the etiology of Recklinghausen's disease but also in the causation of many cases of renal stones, of some cases of renal failure, and of exceptional cases of gastrointestinal disorders.

The parathyroids are the smallest endocrine glands in the body. Four parathyroids are usually found in man, situated on the posterior surface of the thyroid gland; occasionally, fewer than four or more than four have been found. The size of each of these tiny glands varies between 6 and 8 mm. in length, 3 and 4 mm. in width, and 1 and 2 mm. in thickness; they each weigh between 30 and 40 mg. Often, even the expert surgeon, with the most careful dissection, finds it difficult to locate all the parathyroids. Especially aberrant parathyroids, which occur in 10 to 15 per cent of the cases, are often missed because they may be situated anywhere from well above the thyroid gland to deep in the mediastinum. Apart from these ontologic variations, the presence of a goiter is sometimes the cause of one or more of the parathyroids being found in an abnormal location. Total removal of the seemingly insignificant parathyroids is followed by a dangerous and striking syndrome, described in 1855 by Trousseau[38] as tetany. MacCallum and Voegtlin,[22] in 1908, recognized that the rapid decrease of calcium in the serum, following the removal of the parathyroids, was the cause of the tetany. They observed that every time the calcium level in the serum fell below about 6 mg. per 100 cc., cramps appeared.

The arduous task of preparing an active extract from these tiny glands was then begun by many investigators, and finally such preparation was obtained by three investigators working independently (Collip [14]).

When the parathyroids are removed, the calcium level in the serum falls and the inorganic phosphorus level rises. Signs of tetany develop when the calcium value drops below 6 mg. per 100 cc. (normal, 9.5–10.5 mg.). Concurrently, at least if the tetany is due to removal of the parathyroids, the inorganic phosphorus goes up to 5 or 6 mg. per 100 cc. (normal, 3–4 mg.).

The following characteristic signs of parathyroid hyperfunction, i.e., of hyperparathyroidism, can be demonstrated if a parathyroid tumor is present:

1. Increased calcium content of the blood serum (hypercalcemia);
2. Decreased inorganic phosphorus content of the blood serum (hypophosphatemia);
3. Excessive excretion of calcium in the urine (hypercalciuria);
4. Increased excretion of inorganic phosphorus in the urine (hyperphosphaturia);
5. In all cases in which the parathyroid adenoma has caused skeletal changes, the alkaline phosphatase content of the serum is increased.

Albright's[6] concept that parathyroid hormone first lowers the threshold for the excretion of phosphorus in the urine and thereby leads to its increased urinary excretion has now been generally accepted. This hyperphosphaturia results in a decrease of the phosphates of the serum. Since the product of the values of the calcium and phosphorus in the serum tends to remain constant, the lowering of the serum phosphates leads to an increase in the serum calcium, and this in turn is followed by hypercalciuria. In its attempt to increase the calcium content of the serum, the body mobilizes the calcium phosphate of the bones; as a result of this rapid decalcification, osteitis fibrosa sets in. The cycle of events set in motion by the increased phosphate excretion caused by an excess of parathyroid hormone is not the sole mechanism by which this hormone influences bone structure. In addition, the hormone influences bone structure directly, probably because it stimulates the formation and function of the osteoclasts of the bone marrow.

In hyperparathyroidism, the calcium content of the serum is always over 11 mg. per 100 cc., and may even go as high as 23 to 30 mg. In 114 patients with hyperparathyroidism, the calcium value rose above 11 mg. per 100 cc. 109 times, and above 12 mg. 91 times.

The decrease in the inorganic phosphorus content of the serum is somewhat less constant than the hypercalcemia. In 35 out of 79 proved cases of hyperparathyroidism the inorganic phosphorus value was less than 2.5 mg. per 100 cc. Relatively slight renal insufficiency may raise the hypophosphatemia to normal levels.

When there is skeletal involvement in hyperparathyroidism, the alkaline phosphatase content of the serum is increased. It has already been explained that the alkaline phosphatase of the serum runs parallel with the activity of the osteoblasts. In Recklinghausen's disease (hyperparathyroidism with bone involvement), there is not only bone destruction but simultaneous proliferation of osteoblasts and new formation of bone. When, however, hyperparathyroidism leads only to the formation of renal stones or nephrocalcinosis, without apparent bone lesions, the phosphatase level usually remains normal.

In hyperparathyroidism, the urinary excretion of calcium is always greater than normal. Determination of the amount of calcium excreted in the urine on four consecutive days, with the patient on a low calcium intake (Bauer-Aub diet), provides important diagnostic criteria in cases of hyperparathyroidism. Whereas normally 70 to 90 per cent of the excreted calcium is eliminated in the stool, and only 10 to 30 per cent by way of the urine, the reverse is found in hyperparathyroidism; here 70 to 90 per cent of the calcium is eliminated in the urine. On a Bauer-Aub diet, containing 2000 calories and 125 mg. of calcium, normal individuals excrete less than 100 mg. of calcium daily in the urine, while patients with hyperparathyroidism excrete more than 200 mg.

A number of investigators have been able to reproduce experimentally almost all the signs of Recklinghausen's disease by administering excessive amounts of parathyroid hormone to animals. The relation between a parathyroid adenoma and the development of renal stones has also been studied by experimental methods. Guinea pigs were injected with 10 units of parathormone daily for four weeks, and the urethra of each animal was clamped off for seven to twelve hours daily. The combination of an excessive urinary excretion of calcium and of a urinary obstruction led to the formation of renal stones in 3 of the 10 experimental animals.

Frequently, only one enlarged parathyroid is found at the operation of patients with hyperparathyroidism; occasionally, however, there is adenoma formation in more than one parathyroid gland. In 20 cases out of 322 collected by Norris,[26] more than one parathyroid adenoma was found. Aberrant adenomas were present in 30 out of 281 of these cases; in 19 of them the adenoma was located in the mediastinum, in 9 within the substance of the thyroid gland, and in 2 behind the esophagus. The weight of the adenomas varied considerably; the smallest tumor recorded weighed only 0.4 Gm., the largest 120 Gm.

Three different types of cells are present in the parathyroid glands, namely, chief or principal cells, water-clear (Getzowa) cells, and eosinophilic or oxyphilic cells (Welsh cells, or oncocytes of Hamperl). Parathyroid adenomas often consist of a proliferation of chief cells, but they may also be composed mainly of proliferating water-clear cells. Adenomas consisting wholly of oxyphilic cells have been found only in rare cases of hyperparathyroidism. In some cases, all three cell types are in a state of proliferation.

A hyperplasia or hypertrophy of all four parathyroids occurs in some cases of hyperparathyroidism. This generalized hyperplasia consists always of a proliferation of the water-clear cells only, which in such cases are considerably larger than normal and concentrically arranged.

The syndrome of hyperparathyroidism is identical, whether the cause is a tumor of one parathyroid or a hyperplasia of all four parathyroids. Reports of 26 such cases of generalized hyperplasia have appeared in the literature up to 1947. A few cases of hyperparathyroidism due to a malignant tumor of one of the parathyroids have also been described.

The abnormalities of the calcium and phosphorus metabolism caused by hyperparathyroidism may lead to Recklinghausen's bone disease, to nephrolithiasis, to renal failure with or without nephrocalcinosis, or to gastrointestinal complaints.

RECKLINGHAUSEN'S BONE DISEASE

In his original description, von Recklinghausen coined the name "generalized fibrocystic osteitis" to indicate that the disease was characterized by a generalized osteitis fibrosa with softening of the bones, multiple cysts, and giant cell "sarcomas." The normal function of the giant cells of the bones from which these giant cell tumors are derived is to attack and dissolve bone trabeculae. Even benign tumors derived from osteoclasts must therefore infiltrate the bone. While it is true that the giant cells of the tumors in Recklinghausen's disease infiltrate, attack, and destroy the bone tissue, wide experience has proved that these tumors are biologically benign. The designation "giant cell sarcoma" is therefore not an accurate one, and the neutral name "giant cell tumor" should be used.

Giant cell or brown tumors and cysts are frequently, but not invariably, present in Recklinghausen's disease. On the contrary, many typical examples of this disease have been recorded in which neither cysts nor brown tumors could be found.

Cysts and giant cell tumors may disappear spontaneously. They recalcify with remarkable rapidity as soon as the cause of Recklinghausen's disease—the parathyroid adenoma—is removed.

Von Recklinghausen[39] believed that the osteitis fibrosa which he found on microscopic examination of the skeletons of his patients was characteristic of the disease and of fundamental importance for the diagnosis. However, fibrous osteitis, (proliferation of fibrous tissue in the bone marrow and in the haversian canals), is never a primary process. It is a reaction of bone tissue to rapid decalcification, whatever the cause of the decalcification may be. It occurs not only in Recklinghausen's disease, but also in Paget's disease, in polyostotic fibrous dysplasia, occasionally in rickets, in renal osteodystrophy, and in long-standing acidosis, in some patients with Graves' disease, in the vicinity of malignant metastases in the bones, and in other conditions. Osteitis fibrosa is therefore not a disease entity, but merely a sign like fever, anemia, achlorhydria, or other signs.

Generalized osteitis fibrosa is present in Recklinghausen's disease and usually affects all the bones of the skeleton. In some bones, however, the lacunar resorption, recalcification, and fibrous osteitis may be more intense than in the rest of the skeleton. Where the active bone resorption is most extensive, multiple small indentations of the cortex, like halfmoons in shape—so-called scalloping—are found on the roentgenograms. The cortex ultimately resembles old decayed wood full of small pores. Pathologic fractures of the thinned bones lead to angular deformations.

The softening of the spine results in a marked reduction of the body length. Compression of the vertebral bodies by the elastic intervertebral disks leads to the formation of biconcave or so-called fish vertebrae.

The roentgenographic appearance of the skull in Recklinghausen's disease, with its gross-meshed trabeculation and miliary areas of osteoporosis, is often sufficient for the diagnosis of Recklinghausen's disease. Of course, the presence of bone cysts and giant cell tumors greatly aids the diagnosis. Especially the presence of one or more honeycomb-like giant cell tumors in the bones of the skull, in the lower or upper jaw, or in the zygomatic bone, is a strong point for the diagnosis of Recklinghausen's disease, even if the general decalcification is only in the initial stages.

In rare cases, a spontaneous partial cure of hyperparathyroidism may take place. One such case was discovered by Schmorl[30] at autopsy: a parathyroid adenoma the size of a cherry stone was still present.

Recklinghausen's bone disease is characterized by the following symptoms and signs: (1) severe bone pains; (2) generalized osteitis fibrosa; (3) marked skeletal softening, with spontaneous fractures and angular deformation of the bone; (4) frequent presence of giant cell tumors, and cysts; (5) increased calcium in the serum; (6) decreased inorganic phosphorus in the serum; (7) increased urinary content of calcium and phosphorus; (8) increased serum content of alkaline phosphatase; (9) characteristic roentgenograms of the skeleton; (10) frequent bilateral occurrence of renal stones, and disturbed renal function; (11) occasional muscular hypotonia or vomiting; (12) unexplained fatigue, polyuria, palpitations, and dyspnea.

Most of these signs are the direct results of the primary hyperparathyroidism which is always present in Recklinghausen's disease. The presence of a parathyroid adenoma and marked improvement after removal of this tumor should therefore be added to the list of constant findings in Recklinghausen's disease.

The characteristic biochemical syndrome is of the greatest importance in distinguishing typical and atypical cases of Recklinghausen's disease from other skeletal diseases. A diagnosis of Recklinghausen's disease can be excluded if the patient presents extensive decalcification but not the biochemical syndrome. On the other hand, the presence of the biochemical syndrome makes the diagnosis of hyperparathyroidism obligatory, even though extensive decalcification is absent. It must be stressed that in patients with hyperparathyroidism without extensive skeletal involvement the alkaline phosphatase content of the serum may be normal or barely increased. On the other hand, the presence of Recklinghausen's disease is improbable in a patient with extensive bone lesions but with a normal serum content of alkaline phosphatase.

There is general agreement as to the immediate, favorable results following removal of a parathyroid adenoma in patients with Recklinghausen's disease. The hypercalcemia quickly changes after operation to a normal or even to a subnormal calcemia. In most patients after operation the calcium in the serum decreases progressively until tetany develops some two weeks postoperatively, unless calcium and parathormone are administered. In a few exceptional cases the tetany caused by the removal of the parathyroid adenoma has even proved fatal.

The most probable explanation of this postoperative tetany is as follows: After the operation the decalcified skeleton absorbs the calcium from the plasma with such avidity that the flow of the calcium, which because of the hyperparathyroidism was directed from the skeleton to the blood, is reversed to normal. So much calcium is now withdrawn by the skeleton from the blood that hypocalcemia and tetany result. Even the presence of the remaining three normal parathyroids is then insufficient to keep the calcium metabolism in its normal pathways. This concept is supported by the observation that when the phosphatase content of the serum is high, there is greater likelihood of postoperative tetany. The higher the phosphatase value, the more active the osteoblasts, the more calcium is deposited in the bone matrix after operation, the heavier the drain on the calcium circulating in the blood.

Transitory oliguria, which may last for several days, is a frequent occurrence after removal of a parathyroid adenoma. In many patients with Recklinghausen's disease, both kidneys are damaged because of the presence of renal stones and the subsequent pyelonephritis, or because of calcification of the renal tubules. If the daily urinary output of such patients drops to a few hundred cubic centimeters or less, signs of uremia and an increased blood content of nonprotein nitrogen may easily result. Fortunately, within a few days after operation the urinary flow becomes more abundant again and the threatening signs of renal insufficiency rapidly disappear.

Before considering the explanation of this transitory postoperative oliguria, one must first discuss the polyuria which so many of the patients with Recklinghausen's disease have during the active stage of the disease: cases are known in which the urinary output has been as high as 12 and 13 liters per day. The fact that parathyroid hormone, as such, increases the urinary output is well known; injections of parathormone have induced normal diuresis in some patients with cardiac failure and oliguria after many other medications had failed. This diuresis sets in even without concurrent increased urinary excretion of calcium. Evidently, parathyroid hormone has a direct influence upon renal function. This may explain why polyuria is often present in Recklinghausen's disease, a disease in which the parathyroid hormone is released in greater than normal amounts. After operation, the kidneys which have become accustomed to excessive amounts of parathyroid hormone, receive only a normal amount. This normal stimulus for diuresis is small as compared to the overstimulation of the preoperative years, and oliguria consequently develops during the period of accommodation to a normal amount of the hormone.[33, 35]

In most cases, it has been possible to overcome the postoperative period of oliguria by intravenous injections of hypertonic glucose solution and lavish subcutaneous administration of saline solution. Usually, the increase in nonprotein nitrogen in the serum and other signs of renal failure quickly vanish after normal diuresis has been established. The only cases of hyperparathyroidism in which removal of the parathyroid adenoma has been followed by fatal renal failure have been those in which extensive renal involvement and a high serum content of inorganic phosphorus were present preoperatively.

Judging from our own patients, long-standing results of operation in hyperparathyroidism are excellent. Our first patient underwent operation in 1929; he remained well until he died from a coronary thrombosis 10 years later. The second patient was operated on in 1930 and was in excellent condition in 1945, as was a third patient in 1947 who had undergone operation in 1934.

Osteotomy could be performed in one patient four years after operation, and the following data established: (1) the calcium and phosphorus contents of the bones were still 10 per cent lower than normal controls, but the histologic structure had become normal; (2) the haversian canals were no longer enlarged; (3) the marrow fibrosis had completely disappeared.

One author reports that 3 of 12 patients felt completely well thirteen, ten, and five years after operation; 5 patients were considerably improved; 1 was described merely as improved; and 2 patients died, twelve and five years after operation, although considerable improvement was noted.

Nephrolithiasis Due to Hyperparathyroidism with and without Skeletal Involvement

The urinary excretion of abnormal amounts of calcium causes a supersaturation of the urine with calcium salts, especially with calcium phosphates. Mandl,[23] in his original observation, stressed the turbidity of his patient's urine before operation, due to an excessive content of calcium salts. This phenomenon disappeared immediately after the operation. The hypercalciuria explains why renal stones frequently form in patients with hyperparathyroidism. When the urine is alkaline, the stones consist of calcium phosphate, but remarkably often the stones are largely composed of calcium oxalate. In the long run, these stones and the ensuing pyelonephritis often constitute the most dangerous part of the whole syndrome, because they may lead to renal failure.

The generalized osteitis fibrosa, the decalcification and the multiple giant cell tumors and bone cysts must be late manifestations of the disturbance in calcium and phosphorus metabolism due to hyperparathyroidism. The skeleton of an adult contains more than 900 Gm. of calcium. Even when the calcium balance is strongly negative, the daily loss hardly ever exceeds 0.5 Gm. of calcium. Several months, perhaps even years, must elapse before the demineralization of the skeleton can be discovered by roentgenographic examination. Thus, clear-cut renal symptoms and signs, depending on the hypercalcemia and the excess of calcium and phosphorus excreted in the urine, may occur in hyperparathyroidism before the presence of an affection of the skeleton can be noted.

Albright[3] and co-workers were the first to stress the significance of the frequency with which renal stones were found in patients with hyperparathyroidism. When they became convinced that the presenting signs of hyperparathyroidism often consist of renal stones, they began to determine the calcium and inorganic phosphorus values in blood and urine in all of their patients with nephrolithiasis. They were thus able to discover several unsuspected cases of hyperparathyroidism. The urologists in Boston[8, 9, 13] concluded that 3 per cent of the patients who have renal stones suffer from hyperparathyroidism.

One determination of the calcium, phosphorus, and phosphatase levels in the serum is not enough to establish whether the renal stones are due to hyperparathyroidism. The phosphatase value provides no clue, since it remains normal as long as the skeleton is not involved; furthermore, the increase in the serum calcium may be so slight as to make the calcemia seem within normal limits. In addition, it should be remembered that when the proteins of the serum are low, an apparently normal calcemia may in fact represent a hypercalcemia. Much more important is the determination of the urinary calcium excretion, using a Bauer-Aub test diet which is poor in calcium. A daily calcium excretion exceeding 200 mg. is highly suggestive of the presence of hyperparathyroidism.

Barney and Sulkowitch[9] have devised a method which permits a rapid answer to the question of whether an excessive amount of calcium is being excreted in the urine. Their solution, consisting of 2.5 Gm. oxalic acid, 2.5 Gm. ammonium oxalate, 5 cc. glacial acetic acid, and distilled water to make 150 cc., precipitates the calcium in urine which has a slightly acid reaction. Therefore, if the urine is alkaline, addition of acetic acid is necessary. The reagent is mixed with an equal part of urine.

Under normal conditions, a slight precipitation of calcium oxalate occurs. If hypercalciuria exists, the precipitate is thick and milky; as a rule, this also indicates the presence of hypercalcemia.

Certain precautions must be taken in order to assure a correct interpretation of the test. Fasting urine should be taken or, better still, a specimen of the total 24-hour output collected while the patient is on the Bauer-Aub calcium-poor diet. This is advisable because (1) shortly after ingestion of calcium-rich food, especially of milk, the Sulkowitch reaction may be strongly positive, even in normal persons; (2) after drinking large quantities of water, tea, or coffee, the urine may be so diluted that even in patients with hypercalcemia the reaction will be only faintly positive.

If the test is properly done, a strongly positive Sulkowitch reaction in a patient with renal stones certainly indicates the possibility of hyperparathyroidism and necessitates a careful examination of the calcium and phosphorus metabolism.

HYPERPARATHYROIDISM AND NEPHROCALCINOSIS

The hypercalcemia is responsible for the formation of calcium deposits, so-called calcium metastases, in various organs, particularly in the kidneys, the media of the arteries, the myocardium, the lungs, and the mucosa of the stomach and bronchi. Such calcium metastases have even been found in the mesocolon and in the eardrums. They are always present in far advanced hyperparathyroidism. Calcium deposits in the lungs or stomach hardly ever produce clinical signs, although occasionally a little stone or broncholith may be coughed up. One case is known in which the calcifications in the eardrums led to deafness; this disappeared when the calcium deposits were absorbed after removal of the parathyroid tumor.

Even when renal stones do not develop, a parathyroid adenoma may result in renal involvement and renal failure because of multiple calcium precipitations in the collecting tubules and in the interstitial tissue of the pyramids. The calcium infarctions in the kidneys may become so extensive in hyperparathyroidism that they are readily seen on the roentgenograms of the kidneys as calcifications irregularly spread throughout the renal pelvis, renal pyramids, and renal cortex. In other instances, however, these infarctions can only be distinguished with difficulty as a fine stippling on the roentgenograms. Hellström and Wahlgren[17, 18] examined 12 patients with hyperparathyroidism: neither calcifications nor concrements were found in 3 cases, calcifications and concrements in 3 cases, calcifications but no concrements in 4 cases, and concrements but no calcifications in 2 cases. It is now well recognized that when nephrocalcinosis can be visualized on the roentgenograms, a diagnosis of hyperparathyroidism must be considered.

For purposes of differential diagnosis, it should be stressed that other causes, too, may be responsible for nephrocalcinosis. Albright, Dienes, and Sulkowitch[5] have described widespread calcification of the renal pyramids after infection with *Hemophilus influenzae*. Renal calcifications have been repeatedly reported after prolonged administration of large doses of vitamin D. The possibility that sulfonamide derivatives can also cause nephrocalcinosis cannot be disregarded. Tuberculosis and even chronic glomerulonephritis may produce widespread calcification of the renal parenchyma. The presence of nephrocalcinosis limited to the renal pyramids in a rare form of renal failure—so-called lower nephron insufficiency—must also be mentioned. The roentgenologic differential diagnosis between nephrocalcinosis due to lower nephron insufficiency and that due to hyperparathyroidism is usually easy, since in the latter syndrome the calcium deposits are spread throughout the medulla *and* cortex.

Hyperparathyroidism may also lead to the formation of fine calcium precipitates throughout the renal parenchyma, without producing gross nephrocalcinosis. Even if these calcium spicules are so fine that they are not visible on the roentgenograms of kidney and pelvis, they may be the cause of renal insufficiency. In such cases a patient with hyperparathyroidism may present himself as a patient with renal failure. The main roentgenographic diagnostic criteria—skeletal changes, renal stones, and gross nephrocalcinosis—are then absent. Such a patient shows normal or even elevated calcemia, whereas a patient with uremia due to primary renal insufficiency usually shows hypocalcemia. Lièvre's[20] advice to examine the calcium content of the serum in every case of renal failure is therefore justified: these rare cases would otherwise be missed completely.

For the ultimate prognosis of hyperparathyroidism the condition of the kidneys is of far greater importance than the bone lesions. The latter always clear up after operation, the former sometimes grows progressively worse.

GASTROINTESTINAL FORM OF HYPERPARATHYROIDISM

Another infrequent form of hyperparathyroidism consists of lethargy, loss of appetite, nausea, vomiting, and constipation, with or without clear-cut signs of bone involvement. This digestive syndrome depends directly upon the hypercalcemia, which, as experimental evidence has confirmed, may lead to intractable vomiting. When the skeletal affection is still in an initial stage and renal stones have not yet formed, the history and the physical examination of these patients may strongly suggest an abdominal disorder. Only determination of the calcium and phosphorus contents of blood and urine offer a clue leading to the discovery of the hyperparathyroidism. When the skeletal involvement is limited, the phosphatase content of the serum is usually normal.

The signs due to hypercalcemia may be suggestive of duodenal ulcer or even of acute appendicitis. Occasionally, intractable vomiting in a patient with a duodenal ulcer but without signs of pyloric obstruction indicates the presence of hypercalcemia and hyperparathyroidism.

ACUTE HYPERPARATHYROIDISM

A few instances have been recorded of acute and usually fatal exacerbations of hyperparathyroidism. In such cases a sudden aggravation of the hypersecretion of the parathyroid glands leads to the liberation of an even greater amount of parathyroid hormone and results in toxic necrotic lesions of the kidneys.

DISCUSSION

The question why certain cases of hyperparathyroidism lead mainly to skeletal lesions while in others the presenting sign is renal involvement without obvious skeletal changes has been ably discussed by Albright.[1] He has emphasized the importance of the patient's daily diet. Hyperparathyroidism causes the excretion of excessive amounts of calcium phosphate in the urine. If the patient ingests as much calcium as is lost in the urine, then hyperparathyroidism does not lead to marked bone changes, but the urinary calcium excretion is high and there is considerable danger that renal stones or nephrocalcinosis will develop. If the calcium intake is low, hyperparathyroidism will produce a negative calcium balance and the skeletal calcium will be rapidly depleted. The fact that milk is rich in calcium is not without importance in this connection. Thus, in the milk-drinking United States hyperparathyroidism easily leads to renal involvement. In Europe, where adults do not habitually drink milk, hyperparathyroidism will more frequently result in Recklinghausen's bone disease. In general, it may be said that bone lesions are slow to appear, whereas renal stones and nephrocalcinosis develop rather rapidly.

Treatment: surgical intervention is essential in all cases in which the biochemical syndrome of hyperparathyroidism is present. The operation is often simple, but only a surgeon with experience in thyroid and parathyroid surgery can solve the technical problems involved in the removal of aberrant parathyroids. At operation, not only must the tumor be removed but the three normal parathyroids must be visualized to make certain that an adenoma is not being left behind.

If all four parathyroids are hyperplastic, three of them must be removed and the fourth resected until only about 200 mg. of parathyroid substance are left.

Under no conditions should two normal parathyroids be removed when a parathyroid adenoma cannot be found. Such a procedure has no effect whatever on the hyperparathyroidism and creates a difficult problem if a parathyroid adenoma is found at a second operation because the extirpation of the adenoma at that time may lead to fatal tetany. Under these conditions, only a resection of the adenomatous parathyroid is possible.

Treatment of a patient with hyperparathyroidism with large doses of calcium and phosphorus salts is contraindicated. True, the bone pains may improve under this treatment; but the calcium and phosphorus excretion is increased so tremendously that large stones quickly develop in the kidneys.

SUMMARY

Laboratory Findings. Hyperparathyroidism due to the presence of one or more parathyroid adenomas or to a generalized parathyroid hyperplasia leads to hypercalcemia, a decreased serum content of inorganic phosphorus, and an excessive urinary excretion of calcium and phosphorus. An increased alkaline phosphatase content of the blood is found if the hyperparathyroidism has caused skeletal lesions.

The hypercalcemia and hypercalciuria may lead to Recklinghausen's bone disease or generalized fibrocystic osteitis, to renal stones, to renal failure, or to gastrointestinal manifestations.

Clinical Syndrome. Osteitis fibrosa is found in totally different diseases, such as Recklinghausen's bone disease, Paget's disease, renal osteodystrophy, Graves' disease, and experimental acidosis. In Recklinghausen's disease, however, the fibrous osteitis spreads throughout the whole skeleton, and is accompanied by outstanding hyperactivity of the osteoclasts, often resulting in small or large giant cell tumors.

Recklinghausen's bone disease is characterized by severe bone pains, generalized decalcification with osteitis fibrosa, multiple cysts and giant cell tumors, a diffuse atrophy of the corticalis with dilatation of the haversian canals, characteristic roentgenographic changes, the presence of one or two parathyroid adenomas or of generalized hyperplasia of all four parathyroids, and the characteristic biochemical syndrome.

The signs of Recklinghausen's disease disappear after removal of the parathyroid adenoma or after extensive resection of the hyperplastic parathyroids.

Injections of large doses of parathormone into young animals for a long period of time leads to a generalized osteitis fibrosa, with manifestations resembling those of Recklinghausen's disease in man. Renal stones and renal calcifications have also been produced experimentally in animals by the administration of large amounts of parathormone.

The hypercalcemia caused by the parathyroid hyperfunction provokes the formation of calcium metastases in various organs and especially in the interstitial tissue of the kidneys. The hypercalciuria favors the formation of renal stones consisting either of calcium phosphate or of calcium oxalate. Nephrolithiasis occurs in one-third to two-thirds of the patients with Recklinghausen's disease. The resulting pyelitis, and even more the calcium infiltration of the renal tissue, often lead to renal failure.

In many cases, the parathyroid adenoma or the generalized hyperplasia of the parathyroids leads to renal stones or renal failure before bone involvement has become apparent. A parathyroid adenoma is present in about 3 per cent of the patients who apparently suffer from nephrolithiasis only. Unless this adenoma is extirpated, formation of renal stones continues. Gross nephrocalcinosis,—areas of calcification in the renal pelvis and pyramids which are visible on the roentgenogram—suggests hyperparathyroidism. However, a similar nephrocalcinosis also occurs in other diseases, for instance, in lower nephron insufficiency. In the United States, hyperparathyroidism leads more frequently to nephrolithiasis and to renal failure than to Recklinghausen's bone disease. Removal of the parathyroid adenoma is almost always followed by healing of the bone lesions, but the renal failure may continue to progress. In very rare cases, the only sign of hyperparathyroidism is uncontrollable vomiting. Careful analysis of serum and urine, combined with roentgenographic examination of the skeleton, must be a routine procedure in all patients with nephrolithiasis, uremia, and vomiting of unexplained origin. Determination of the urinary calcium excretion after a calcium-poor diet is a more sensitive test for the possible presence of hyperparathyroidism than the serum analyses for calcium and inorganic phosphorus. Hyperplasia of all four parathyroids, consisting of prolification of water-clear cells, leads to the same syndrome as does the presence of a solitary parathyroid adenoma.

Extirpation of the parathyroid adenoma may be difficult if the adenoma is situated in an aberrant gland. In about 10 per cent of the cases, 2 adenomas, and occasionally 3, are found. They must all be removed if a cure is to be obtained. In the patients with a generalized parathyroid hyperplasia, 3 of the hyperplastic glands must be removed and a subtotal resection of the fourth performed. Less than 200 mg. of parathyroid tissue should be left.

Postoperatively, the calcium and inorganic phosphorus values of the serum return to normal. The urinary calcium output also drops, usually below normal. The bone pains of the patients with Recklinghausen's disease disappear, and new bone forms. A remarkable recovery sets in, practically leading to a complete cure and most patients are able to resume their daily occupations. In 3 of our cases, this cure lasted for fifteen, thirteen, and ten and a half years, respectively. The formation of renal stones is halted but the renal failure, at least in some instances, is progressive.

Tetany may occur immediately after operation because the decalcified skeleton absorbs calcium so rapidly as to produce hypocalcemia. This postoperative tetany is nearly always temporary. Oliguria is frequent in the first postoperative days.

4. Parathyroid Hyperplasia, Secondary to Other Diseases

Even before Mandl[23] had proved that a primary parathyroid adenoma leads to hyperparathyroidism and often to skeletal disease, it had been known that the reverse also occurs, that is, that parathyroid hyperplasia may develop consequent to a decalcifying disease. In 1907, Erdheim[14] had reported hyperplasia of the parathyroids in 3 cases of osteomalacia, and he and others described a similar parathyroid hyperplasia in children with rickets and in rats with experimental rickets. In later years, parathyroid hyperplasia in chronic renal failure has been observed frequently. This has also been reported in at least 2 cases of multiple myeloma with hypercalcemia associated with parathyroid enlargement, and in an occasional case of widespread skeletal metastases of a malignancy.

In most cases of extensive decalcification with secondary hyperplasia of the parathyroids, all 4 glands are hyperplastic.

PARATHYROID HYPERPLASIA IN EXPERIMENTAL AVITAMINOSIS D

Experimental data point to the frequent occurrence of secondary parathyroid hyperplasia in avitaminosis D. In chickens, such avitaminosis leads to decalcification of the bones and concomitant parathyroid hyperplasia. Sheard[32] and co-workers kept chickens in cages of amber glass. This glass filtered out all the ultraviolet and most of the violet rays. The chickens were given a diet containing a sufficient but not an excessive amount of vitamin D. Under these experimental conditions, decalcification of the skeleton and considerable hyperplasia of the parathyroids developed; the parathyroids of these chickens weighed 53 mg., as compared to a weight of 5 mg. in normal controls.

Addition of cod liver oil to the diet of these animals prevented the parathyroid hyperplasia, even when they were kept in the amber-glassed cages. Daily irradiation with ultraviolet rays for 10 to 15 minutes and administration of small doses of parathormone had the same effect. These observations have been confirmed repeatedly.

Chinese workers[12] have studied the parathyroid hyperplasia which develops in rats placed on a special vegetarian diet. Addition of vitamin D to the diet prevented the parathyroid hyperplasia. Addition of calcium, without administration of vitamin D, had the same effect; vitamin D, however, was the more effective agent.

BONE LESIONS AND PARATHYROID HYPERPLASIA IN CHRONIC RENAL FAILURE

Secondary parathyroid hyperplasia occurs in renal failure with fair frequency. In the same condition extensive osteitis fibrosa is occasionally found. However, in some cases of renal failure marked parathyroid hyperplasia is present without bone lesions. Therefore the parathyroid changes and the bone lesions occurring in uremia should be discussed separately.

Ample experimental evidence indicates that there is a close relationship between renal insufficiency and parathyroid hyperplasia. Unilateral nephrectomy in rats and removal of part of the other kidney with a thermocautery lead, via the resulting nephritic changes in the kidney remnant, to a hypertrophy of the parathyroids. Bone changes develop, which sometimes resemble osteitis fibrosa, sometimes those of rickets.

Postmortem observations also indicate that parathyroid hyperplasia may develop in renal insufficiency. Bergstrand,[10] in 1921, reported that he had found enlarged parathyroid glands in 10 out of 50 cases of chronic glomerulonephritis. Other authors have reported comparable figures. In the majority of patients with chronic uremia the combined weight of all 4 parathyroids greatly exceeds the average normal weight of 120 to 140 mg. Nevertheless, although the above figures give clear evidence of the frequency of parathyroid hyperplasia in renal failure, it should be emphasized that in a considerable number of such patients the parathyroids do not increase in size, even when the chronic uremia has resulted in extensive bone lesions.

From present knowledge, it seems certain that hyperplasia of the parathyroids develops in patients with renal insufficiency if the renal failure is of long duration and has given rise to acidosis. The parathyroid hyperplasia may result in the formation of tumors weighing several grams each. Often, but not always, skeletal changes develop at the same time, sometimes accompanied by calcification of the media of the arteries or by calcium phosphate incrustations in the soft tissues. Calcification of the arterial media has been observed in children as young as 6 and 7 months and 2 years who were suffering from interstitial nephritis and parathyroid hyperplasia.

The mechanism by which chronic renal insufficiency with acidosis can lead to a generalized parathyroid hyperplasia has been variously explained. At first, it was suggested that in chronic renal failure the hyperphosphatemia acts as a stimulus for the parathyroids. In recent years, not the hyperphosphatemia but the accompanying hypocalcemia is regarded as the most important factor in the causation of the parathyroid hyperplasia. Hypocalcemia also accounts for the parathyroid hyperplasia which occurs in chronic biliary fistula, in osteomalacia and rickets in man, in experimental rickets in chickens, and in vegetarian rats. In all these instances, the serum content of calcium is decreased and the inorganic phosphorus is low or normal.

Examination of the biochemical data in the published reports of cases of renal insufficiency and parathyroid hyperplasia reveals that the serum content of calcium is often not significantly decreased in these patients. Several of them even showed a temporary or continuous slight hypercalcemia. Possibly, the uremic hypocalcemia which first gave rise to the hyperplasia of the parathyroids was changed, under the influence of this secondary hyperplasia, to a normal calcemia.

HISTOLOGY OF PARATHYROID HYPERPLASIA IN RENAL INSUFFICIENCY

The hyperplasia of the parathyroids in patients with rickets or renal failure involves all four parathyroids, and may be due to proliferation either of water-clear cells or of chief cells. There are various diagnostic criteria which permit the differentiation between primary hyperparathyroidism, as it exists in Recklinghausen's disease, and secondary hyperplasia of the parathyroids, such as is found in uremia. These criteria are: (1) The presence of one or two parathyroid adenomas favors the diagnosis of primary hyperparathyroidism. (2) The presence of a generalized parathyroid hyperplasia consisting exclusively of chief cells is usually caused by chronic renal failure. (3) Marked hypercalcemia indicates the presence of primary hyperparathyroidism. (4) Hyperplasia of all four parathyroids due to proliferation of water-clear cells can be found in both primary hyperparathyroidism and secondary hyperplasia resulting from chronic uremia. In the former condition, large water-clear cells only are found, while in chronic uremia even when the water-clear cells are present in excessive numbers they are always accompanied by young chief cells.

Despite these criteria, it may occasionally be difficult to decide whether a given case is a primary disease of the skeleton with secondary hyperplasia of the parathyroids, or whether the adenoma is primary and the skeletal changes secondary.

Parathyroid hyperplasia has repeatedly been observed in patients with one or more pituitary adenomas.

RENAL OSTEODYSTROPHY OR RENAL OSTEOFIBROSIS

In many children and young adults suffering from congenital bilateral dilatation of the ureters and renal pelvis, from congenital hypoplasia of the kidneys, or, occasionally, from chronic glomerulonephritis, not only parathyroid hyperplasia but also skeletal changes are found. Bone lesions occur only when azotemia and acidosis have persisted for a long time. This syndrome was formerly called renal rickets. However, since the bone lesions usually consist of widespread osteitis fibrosa, the condition is more correctly designated as renal osteodystrophy, renal osteofibrosis, or osteonephropathy. Whether the term "renal hyperparathyroidism" is correct remains to be seen.

It has now become clear that bone lesions which develop in children affected by the rare syndrome of lower nephron insufficiency with hyperchloremia, hypocalcemia, and acidosis due to tubular dysfunction, are similar to osteomalacic manifestations, and must therefore be distinguished from renal osteofibrosis, as seen in chronic renal failure.

The roentgenographic bone lesions in juvenile cases of renal osteodystrophy vary between (1) stunted growth or renal dwarfism, sometimes accompanied by true infantilism; (2) generalized decalcification; and (3) decalcification with swelling of the epiphyseal disks, producing roentgenographic lesions suggestive of rickets.

The translucency of the shafts of the long bones and their porous appearance is much more marked in advanced cases of renal osteodystrophy than in rickets. The roentgenograms of the distal parts of the diaphyses present irregular metaphyseal margins, whereas the epiphyseal end is well-defined. Occasionally, the roentgenograms reveal the presence of large and deeply cupped metaphyses, which often have a woolly appearance. Subperiosteal erosion of the bone of the metaphysis is not uncommon, together with generalized decalcification. It is no wonder that epiphyseal slipping frequently occurs in these patients. The woolly appearance of the epiphyses is so typical that when this roentgenographic lesion is found, the diagnosis of renal osteofibrosis is justified. As a rule, the skeletal changes are best seen at the knees, wrists, and ankles.

Usually, the epiphyseal disks of patients with renal osteodystrophy remain open, even in the rare patient who attains adult age. Improvement of the roentgenographic signs in the cases of renal osteodystrophy which show cupped metaphyses and a woolly appearance is rare.

The character of the skull changes is particularly noteworthy. When the rest of the skeleton shows general decalcification, the skull usually appears moth-eaten, and sometimes shows fine or coarse stippling. Ultimately, roentgenograms may be obtained resembling those of the skull in Paget's disease. As mentioned above, in juvenile patients with renal osteopathy the parathyroid hyperplasia sometimes gives rise to large parathyroid tumors.

The frequency of renal osteodystrophy in children must be partly related to the long duration of the uremia which is caused by congenital anomalies of the kidneys. At the same time, it should be remembered that bone changes generally develop more easily in the young, growing skeleton than in the adult one. The experimental production of osteitis fibrosa by ammonium chloride administration, by lead intoxication, by parathormone injections, and by other agents is also much more readily obtained in young animals than in older ones. Occasionally, renal osteodystrophy also develops in adults with long-standing uremia. In such cases calcium deposits in the neighborhood of the joints, extreme calcification of the media of the arteries (Mönckeberg's type of arteriosclerosis), and generalized osteitis fibrosa, together with an enormous enlargement of all four parathyroids, are found. The retention of acidic substances, which is a constant finding in chronic uremia, must be an important etiologic factor in the destructive osteitis fibrosa found in renal osteodystrophy.

Occasionally, a certain degree of impaired calcification of osteoid zones is found in renal osteodystrophy. This may explain the seemingly rachitic changes reported in the older literature. The poorly calcified osteoid zones in renal osteodystrophy, however, must be considered as a secondary sign, related to the poor absorption of calcium from the intestine. In uremia, the phosphates cannot be excreted by the diseased kidneys and the intestine becomes the main route for their elimination. The presence of excessive amounts of phosphates in the intestine results in the formation of insoluble calcium phosphate. The absorption of calcium from the intestine is thereby impaired, and a certain lack of calcification of the osteoid zones results. In renal osteofibrosis, the presence of noncalcified osteoid is only of secondary importance, and the primary skeletal lesion consists of osteitis fibrosa following destruction of bone by acidosis. It follows that, in contradistinction to genuine rickets, there is hardly a case of renal osteodystrophy which reacts favorably to administration of vitamin D.

It is highly improbable that renal osteodystrophy is caused mainly by the hyperphosphatemia which, in the Occident, is a nearly constant sign of uremic acidosis. In Northern China, chronic renal insufficiency with extensive renal osteodystrophy occurs commonly. In the Far Orient, the phosphorus intake with the food is low, and uremic patients, although acidotic as shown by the decreased carbon dioxide content of the serum, do not present hyperphosphatemia.[34, 35] One must therefore conclude that the important factor in the production of renal osteodystrophy is the acidosis rather than the hyperphosphatemia.

RENAL HYPERPARATHYROIDISM

It should be repeated that in many cases of chronic renal failure marked parathyroid hyperplasia has been found in the absence of osteitis fibrosa. On the other hand, in chronic renal insufficiency marked parathyroid hyperplasia and generalized osteitis fibrosa frequently occur together and the designation "renal hyperparathyroidism" has lately become popular.

However, there is not definite proof of the presence of hyperfunction of the parathyroids in patients with renal osteopathy even if marked parathyroid hyperplasia is present. Some authors, by means of special technics, were able to demonstrate an excess of parathyroid hormone in the blood of their patients with renal osteofibrosis, but these findings have not been generally confirmed. Furthermore, neither the clinical nor the metabolic pictures of renal osteodystrophy agree wholly with that of hyperparathyroidism. Albright[7] has pointed out that the delayed closure of the epiphyseal disks—a nearly constant sign of renal osteodystrophy—cannot be explained on the grounds of hyperparathyroidism. Large amounts of calcium are excreted in the urine in primary hyperparathyroidism, even when secondary renal insufficiency sets in. In renal osteodystrophy, on the other hand, the urinary calcium excretion is low. Thus, there are strong indications that factors other than parathyroid hyperfunction must be instrumental in the production of the generalized osteitis fibrosa found in long-standing renal failure.

Treatment: renal failure leads to bone lesions or hyperplasia of the parathyroids only in the terminal stages of the disease. By that time it is usually impossible to improve renal function. However, the impairment of calcium absorption, which is mainly due to the presence of excessive amounts of phosphates in the intestine, can occasionally be relieved by large doses of aluminum in the form of amphojel, 1 teaspoonful every three hours. By this means, aluminum phosphate is formed in the intestine, and calcium is left free to be absorbed. Then the calcium content of the serum increases and the general condition is at least temporarily improved. Iron salts, (0.5 Gm. of reduced iron, thrice daily or 0.5 Gm. of iron and ammonium citrate twice daily in capsules) can be given instead of the amphojel. Needless to say, any relief obtained is only temporary.

SUMMARY

Whereas a parathyroid adenoma is the cause of Recklinghausen's disease and of other forms of hyperparathyroidism, in other diseases with extensive skeletal decalcification the situation is exactly reversed. Here a secondary hyperplasia of the parathyroids may develop as the reaction to the abnormal calcium and phosphorus metabolism.

Experimental hyperplasia of the parathyroids has been obtained (1) in experimental avitaminosis D in chickens, by exclusion of ultraviolet light and by deprivation of vitamin D; (2) in dogs with complete biliary fistula; (3) in rats with chronic renal insufficiency.

In man, this secondary hyperplasia of the parathyroids may occur (1) in osteomalacia; (2) as an extreme exception, in multiple myeloma and in generalized malignant metastases in the bones; (3) in chronic renal failure with acidosis and, commonly, with phosphate retention. This is especially the case in children and young adolescents with congenital lesions of the kidneys and changes in the skeleton. The same picture has also been observed, though rarely, in adults with exceptionally long-standing renal failure. This secondary hyperplasia of the parathyroids in chronic uremia may be due to proliferation of the chief cells or of the water-clear cells.

The bone lesions found under these circumstances usually consist of osteitis fibrosa and should be designated as renal osteofibrosis or renal osteodystrophy. Not infrequently at autopsy of uremic patients hyperplasia of parathyroids is found in the absence of skeletal lesions. It seems probable that it is the hypocalcemia which stimulates the parathyroid hyperplasia. Occasionally, a certain amount of osteoid is found around the bone trabeculae. This is only a secondary process, and is related to the impaired calcium absorption from the intestine in uremia. Despite the occasional occurrence of osteoid zones, the designation of renal rickets should be considered erroneous. This holds true even though in children and young adolescents with chronic renal failure the closure of epiphyseal disks is delayed and roentgenographic changes resembling those of rickets are sometimes seen. The term “renal osteofibrosis” or “osteonephropathy” is the correct one. The term “renal hyperparathyroidism” has recently been proposed, but it has certainly not been proved that hyperfunction of the enlarged parathyroids plays an important role in the causation of the generalized osteitis fibrosa which is often found in these cases.

Severe acidosis but practically no phosphate retention occurs in the renal osteodystrophy observed in North China. It seems probable that the low phosphorus content of the Chinese diet is the reason why the inorganic phosphorus of the blood remains within normal limits in uremia. This observation favors the conclusion that not the hyperphosphatemia but the acidosis is the cause of renal osteofibrosis.

LABORATORY FINDINGS

The findings in secondary parathyroid hyperplasia due to avitaminosis D or to a chronic biliary fistula have already been discussed.

The outstanding signs in chronic renal failure are hypocalcemia, acidosis, and usually hyperphosphatemia. In cases with extensive parathyroid hyperplasia, the calcium of the serum is often normal or low normal. It seems possible that the secondary hyperplasia of the parathyroids is responsible for the change from the original hypocalcemia to a normal calcemia.

REFERENCES

1. Albright, F. Parathyroids: Physiology and therapeutics. *J.A.M.A.* 117:527, 1941.
2. Albright, F. Cushing's syndrome. *Harvey Lect.* 38:123, 1942–43.
3. Albright, F., Baird, P. C., Cope, O., and Bloomberg, E. Studies on the physiology of the parathyroid glands: IV., Renal complications of hyperparathyroidism. *Am. J.M.Sc.* 187:49, 1934.
4. Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., Jr., and Roos, A. Osteomalacia and late rickets. *Medicine* 25:399, 1946.
5. Albright, F., Dienes, L., and Sulkowitch, H. W. Pyelonephritis with nephrocalcinosis caused by H. influenzae and alleviated by sulfanilamide. *J.A.M.A.* 110:357, 1938.
6. Albright, F., and Ellsworth, R. Studies on the physiology of the parathyroid glands: I., Calcium and phosphorus studies of a case of idiopathic hyperparathyroidism. *J. Clin. Investigation* 7:183, 1929.
7. Albright, F., and Reifenstein, E. C. The Parathyroid Glands and Metabolic Bone Disease. Baltimore, Williams & Wilkins, 1948.
8. Barney, J. D., and Mintz, E. R. The relation of the parathyroid glands to urinary lithiasis. *Brit. J. Urol.* 8:36, 1936.
9. Barney, J. D., and Sulkowitch, H. W. Progress in the management of urinary calculi. *J. Urol.* 37:746, 1937.
10. Bergstrand, H. (*a*) The parathyroid bodies and Bright's disease. *Acta med. scandinav.* 53:644, 1921. (*b*) Parathyroidstudien: II., Über Tumoren und hyperplastische Zustände der Nebenschilddrüsen. *Acta med. scandinav.* 54:529, 1921. (*c*) Ostitis fibrosa generalisata Recklinghausen mit pluriglandulärer Affektion der innersekretorischen Drüsen. *Acta med. scandinav.* 76:128, 1931.
11. Buchbinder, W. C., and Kern, R. Experimental obstructive jaundice: I., Growth factor in defective calcification. *Arch. Int. Med.* 40:900, 1927.
12. Chang, C. Y., and Chen, T. T. Parathyroid hypertrophy and hypocalcemia in vegetarian rats. *Chinese J. Physiol.* 15:19, 1940.
13. Chute, R. Clinical aspects of hyperparathyroidism with special reference to urology. *J. Urol.* 41:762, 1939.

14. Collip, J. B. The extraction of a parathyroid hormone which will prevent and control parathyroid tetany and which regulates the level of blood calcium. *J. Biol. Chem.* 63:395, 1925.

15. Ellsworth, R. Studies on the physiology of the parathyroid glands. V. Action of parathyroid extract on the renal threshold for phosphorus. *J. Clin. Investigation* 11:1011, 1942.

16. Erdheim, J. (*a*) Tumor des Epithelkörperchens. *Beitr. z. path. Anat. u. z. allg. Path.* 33:214, 1903. (*b*) Über Schilddrüsenaplasie. *Beitr. z. path. Anat. u. z. allg. Path.* 35:366, 1904. (*c*) Über Epithelkörperbefunde bei Osteomalacie. *Sitzungsber. d. k. Akad. d. Wissensch., Math.-naturw. Th.* 116:311, 1907. (*d*) Morphologische Studien über die Beziehungen der Epithelkörperchen zum Kalkstoffwechsel. *Frankfurt. Ztschr. f. Path.* 7:175, 1911. (*e*) Rachitis und Epithelkörperchen. Wien, 1914. (*f*) Pathologische Anatomie bei Rachitis und Osteomalazie. *Wien. klin. Wchnschr.* 41:1544, 1928.

17. Gley, E. Sur les effets de l'extirpation du corps thyroïde. *Compt. rend. Soc. de biol.* 43:551, 1891.

18. Hellström, J. Hyperparathyroidism and ostitis fibrosa generalisata. *Acta chir. scandinav.* 69:237, 1932.

19. Hellström, J., and Wahlgren, F. Hyperparathyroidism: clinical and pathological observations of 12 cases. *Acta chir. scandinav.* 91:472, 1944.

20. Higgins, G. M., Sheard, C., and Wilder, R. M. The effects of ultraviolet radiation on rachitic chickens. *Proc. Staff Meet. Mayo Clin.* 8:780, 1933.

21. Kienböck, R. Über die Pagetsche Knochenkrankheit und Epithelkörperchentumoren. *Bruns Beitr. z. klin. Chir.* 159:597, 1934.

22. Kohn, A. Studien über Schilddrüse. *Arch. f. mikrosk. Anat.* 44:366, 1895.

23. Lièvre, J. A. (*a*) L'ostéose parathyroïdienne et les ostéopathies chroniques. Paris, Masson, 1932. (*b*) Ostéite déformante de Paget et traumatisme. *Presse méd.* 44:45, 1936.

24. Looser, E. Ostitis deformans Paget. *Lehrbuch der Röntgendiagnostik* (Schinz, Baensch & Friedl) 3. Aufl., 1:215, 1932.

25. MacCallum, W. G., and Voegtlin, C. (*a*) On the relation of the parathyroid to calcium metabolism and the nature of tetany. *Johns Hopkins Hosp. Bull.* 19:91, 1908. (*b*) On the relation of tetany to the parathyroid glands and to calcium metabolism. *J. Exper. Med.* 11:118, 1909.

26. Mandl, F. (*a*) Therapeutischer Versuch bei einem Falle von Ostitis fibrosa generalisata mittels Exstirpation eines Epithelkörperchentumors. *Zentralbl. f. Chir.* 53:260, 1926. (*b*) Die Funktionserkrankungen der Epithelkörper. *Wien. klin. Wchnschr.* 51:67;106, 1938. (*c*) Klinisches und Experimentelles zur Frage der lokalisierten und generalisierten Ostitis fibrosa. *Arch. f. klin. Chir.* 143:1, 1926. (*d*) Authentischer Bericht über den ersten, mit Epithelkörperchen-exstirpation behandelten

Fall von Recklinghausenscher Krankheit. *Bruns Beitr. z. klin. Chir.* 160:295, 1934. (*e*) Die Kalkstoffwechsel und seine Beziehungen zur Chirurgie der Epithelkörperchen. *Bruns Beitr. z. klin. Chir.* 162:643, 1935.

27. Mandl, F., and Uebelhör, R. Parathormon—Ostitis fibrosa—Nierenstein (Experimentelle Studie). *Zentralbl. f. Chir.* 60:68, 1933.
28. Miles, L. M., and Feng, G. T. Calcium and phosphorus metabolism in osteomalacia. *J. Exper. Med.* 41:137, 1925.
29. Milkman, L. A. Pseudofractures (hunger, osteopathy, late rickets, osteomalacia). *Am. J. Roentgenol.* 24:29, 1930.
30. Milkman, L. A. Multiple spontaneous idiopathic symmetrical fractures. *Am. J. Roentgenol.* 32:622, 1934.
31. Norris, E. H. (*a*) Primary hyperparathyroidism. *Arch. Path.* 42:261, 1946. (*b*) The parathyroid adenoma: a study of 322 cases. *Surg., Gynec. & Obst.* 84: *Internat. Abster. Surg.* 1, 1947.
32. Pommer, G. Untersuchungen über Osteomalacie und Rachitis. Leipzig, Vogel, 1885.
33. Pompen, A. W. N., La Chapelle, E. H., Groen, J., and Mercx, A. P. M. Hungerosteopathy (osteomalacia) in the Netherlands. *Amsterdam, Wetenschappelyke Vitgevery,* 1946.
34. von Recklinghausen, F. D. (*a*) "Die fibröse oder deformirende Ostitis, die Osteomalacia und die osteoplastischen Carcinose in ihren gegenseitigen Beziehungen," in: *Festschrift . . . Rudolf Virchow zu seinem 71.* Geburtstage, Berlin, 1891, p. 3. (*b*) Untersuchungen über Rachitis und Osteomalacie. Jena, Fischer, 1910.
35. Sandström, I. [Ueber eine neue Drüse beim Menschen und bei verschiedenen Säugethieren.] *Upsala läkaref. förh.* 15:441, 1880; German abstract in *Schmidt's Jahrb.* 187:114, 1880.
36. Schmorl, O. Über Ostitis deformans Paget. *Virchows Arch. f. path. Anat.* 283:694, 1932.
37. Sheard, C., Higgins, G. M., and Foster, W. I. The growth and development of chicks as influenced by solar radiation of long visible and ultraviolet wave lengths. *Am. J. Physiol.* 94:84, 1930.
38. Snapper, I. Parathyroid tumor and changes of the bones. *Arch. Int. Med.* 46:506, 1930.
39. Snapper, I. Chinese Lessons to Western Medicine. New York, Interscience, 1941.
40. Snapper, I. Medical Clinics on Bone Disease. New York, Interscience, 1943.
41. Sussman, M. L., and Copleman, B. The roentgenographic appearance of the bones in Cushing's syndrome. *Radiology,* 39:288, 1942.
42. Theiler, A. The osteodystrophic diseases of domesticated animals. 3. Osteodystrophia fibrosa. *Veterinary J.* 90:183, 1934.
43. Trousseau, A. Cliniques médicales de l'Hôtel-Dieu de Paris (ed. 11). Paris, Baillière, 1913.

Chapter 11

IRON MALNUTRITION

R. F. Farquharson

Although iron is said to have been in common use in the treatment of disease since ancient times, its efficacy was long related to the planetary influence of Mars and only in recent centuries has there been any clear conception of its value. Sydenham (1661) and Willis (1681) described the beneficial effect of administration of its inorganic salts in cases of chlorosis.[5] Almost one hundred years later Menghinis discovered that iron was an integral constituent of red blood cells. In 1832, Fodisch found that blood iron was decreased in anemias of young girls.[5] A few years later, Ashwell[2] (1836) clearly recognized chlorosis as a specific entity rather than a symptomatic anemia. He described its occurrence, usually in adolescence but also at subsequent periods, in delicate, nervous girls with a poor appetite, a dislike for meats, and an inadequate diet. He noted the symptoms characteristic of anemia, the occasional occurrence of thin, brittle nails, and the good response to ingestion of inorganic iron salts with recovery in the absence of complications such as tuberculosis. He considered that "a morbid peculiarity of constitution, of which anemia is the prominent symptom, lies at the basis of the disease," and postulated that "the deteriorated quality of the blood, and its defective quantity, may both owe their origin to defective digestion and nutrition."

In the latter half of the nineteenth century the introduction of methods of estimating hemoglobin and counting blood cells stimulated the study of anemias and led to the recognition[25] that the red blood cells of chlorotic girls were small and pale and that the deficiency in hemoglobin in chlorosis was greater than the reduction in the number of red blood cells, i.e., that it was a hypochromic anemia. It was universally accepted at this time that iron was a specific remedy for the disease. Thus Allbutt,[1] paraphrasing the words used by Osler with reference to the administration of quinine in malaria, could say that "the physician who cannot treat chlorosis successfully with iron should abandon the practice of medicine"; and Osler[25] remarked that "it really does not make much difference what form (of iron) is employed so long as enough is administered,"—he himself advised administration of five grains of ferrous sulphate in Blaud's pills two or three times a day.

Yet the nature of chlorosis was far from clear and many theories were advanced to explain its cause. With his native shrewdness, Allbutt remarked that, although yet unknown, the causation of chlorosis was probably simple. But the conception that this anemia was a manifestation of deficiency of iron was not generally recognized for several decades, while there continued to be great speculation about the mechanism of cure under iron therapy. Stockman,[28-31] however, clearly pointed the way when, in a series of papers (1893-1896), he emphasized excessive menstruation or other blood loss and insufficient supply of food as the two important factors which directly bring on the anemia. He pointed out that chlorotic girls, from poor diet, have inadequate iron stores and cannot well replace blood lost by hemorrhage. The loss of blood further depletes the iron stores, both factors having a greater effect in the period of rapid adolescent growth. With clear insight he noted that the anemia of the menopause, in which the blood picture and symptoms were similar to those presented by chlorotic girls, was palpably due to dyspepsia, insufficient food, and blood loss. In addition to these two main factors, he also suggested that certain women have an inherent tendency to suffer from this type of anemia.

Unfortunately the great majority of physicians of his day held no such clear conception, and it was generally believed that iron had a peculiar stimulating effect on the blood as a tissue. About the same time the idea was advanced[1] that organic preparations were more effective than inorganic salts and, although this theory was soon disproved, it had a prolonged, unfavorable influence on the pharmaceutical manufacturers and on medical practice. Furthermore, extensive experimental work on anemia in the early part of the twentieth century failed to demonstrate the value of iron therapy because the experimental anemias studied were not of the hypochromic iron-deficiency type and, of course, were not affected by the administration of iron. These experimental findings so influenced many clinical teachers of this period as to lead to a widespread belief that iron was of little or no value in treatment of any type of anemia, an idea never generally accepted by practicing physicians. One must remember, however that, up to this time, in spite of Stockman's work, it had never been appreciated that iron was of value only in a nutritional sense and that in relief of anemia its action was to provide a building stone for the manufacture of hemoglobin. Furthermore, possibly because of the general adoption of better diet and improvement in hygienic conditions of adolescent girls, chlorosis seemed almost to disappear.

In the 1920's physicians began once more to stress the importance of iron and, among others, Meulengracht[21] emphasized the value of administration of large doses of its inorganic salts as a specific therapy in hypochromic types of anemia. About the same time Whipple and his associates[33] demonstrated in anemic dogs that administration of iron was of value only when there was an actual need for the element, as when the iron stores had been exhausted by repeated bleeding. The discovery in 1926 of liver therapy for pernicious anemia greatly stimulated interest in blood diseases and the search for specific remedies for different types of anemia. By the mid-1930's the work of numerous investigators, and particularly of Clark Heath and his associates[18] in Minot's clinic, had firmly established the belief that factors leading to an insufficient supply of iron at any age and in both sexes will cause a specific hypochromic type of anemia which is quickly relieved by iron therapy and that, under such circumstances, the effects of assimilated iron may be expressed quantitatively as newly-formed hemoglobin. The increased knowledge of iron metabolism in recent years, augmented by the experimental use of radioactive isotopes, has confirmed this belief.[3, 11, 15, 17, 20, 33] But much is yet to be learned about the nature of the factors that control absorption[12, 13] and storage of iron and its intermediary metabolism.

METABOLISM OF IRON

THE IRON CONTENT OF THE BODY

It is difficult to make any precise statement about the total iron content of the body. All workers are in agreement, however, that the greater part of the body's iron is found in the hemoglobin of the red blood cells and of the muscle. Shohl[27] has estimated that there are about 4.5 Gm. of iron in the body of a 70-Kg. man and that of this amount about 2.9 Gm. are contained in the blood, 1.5 Gm. in muscle hemoglobin, and smaller amounts in the liver, spleen, and remaining tissues. His figure for muscle hemoglobin may be too high. In dogs, Hahn[14] reports the blood hemoglobin to contain 57 per cent, muscle hemoglobin 7 per cent, parenchyma iron 16 per cent, and available storage iron 20 per cent. Heath and Patek[18] and Granick[12] estimate that 55 per cent of the iron is in the circulating blood, 10 per cent in muscle hemoglobin and heme catalysts, and 30 to 35 per cent as a storage fraction. The amount stored in liver, spleen, and bone-marrow, and available for use in the manufacture of blood hemoglobin in case of hemorrhage, probably varies greatly. That it may be of considerable magnitude is shown by the fact that after large hemorrhages, amounting to one-half or more of the circulating blood, the hemoglobin of previously healthy patients will often rise spontaneously to normal levels in a few weeks' time without administration of iron.

The importance of iron in the transportation of oxygen to the tissues by the blood hemoglobin is generally appreciated. That it is an essential constituent of all other cells is less commonly realized. This was early pointed out by Macallum[19] (1894) when he stated that "the discovery of microchemical methods for detecting iron in cells has aided me in establishing the generalization that the most important of all elements in the life of every cell is an iron-holding compound." The amount required by the cells of the body in general is relatively small, amounting probably to not more than one-third of a gram in a 70-Kg. adult. This parenchyma iron is essential, however, for the metabolism of the cells and is unavailable for blood formation; it is conserved by the body and, like the iron of muscle hemoglobin, is probably not decreased even in states of severe iron deficiency.[17] It is the iron contained in blood hemoglobin and in the stores in the liver, spleen, and bone-marrow, which in adults with a large reserve may amount to four grams or more, that is depleted in patients with iron malnutrition.

The Physiologic Tissue Requirements of Iron

The supply of iron required by the healthy body varies greatly with age and sex. From birth to puberty it is essentially the same for both sexes, namely, the requirement for growth. After puberty the female requires iron to make up for the losses in menstruation, pregnancy, and lactation. In both sexes the need will increase with hemorrhage from any source. The quantitative aspects of the tissue requirements for growth are clearly shown by data collected by Heath and Patek[18] which, as the authors point out, are at best only approximations. Starting with about 500 mg. of iron in the fetus (170 mg. in the circulating blood), the child increases its body iron by nearly 200 mg. in the first year of life, and by from 70 to 100 mg. per year for the next nine years. In the teens the retention increases greatly, reaching 300 mg. or more per year at the height of adolescent growth, then rapidly falling off, the adult level being attained by 21 years. Because of the loss of iron from the body in menstruation, pregnancy, and lactation, a woman will need over 12 Gm. from birth to 47 years of age as opposed to about 3 Gm. for the male. These figures have to do with actual tissue needs, largely exclusive of the variable iron stores, and of course do not indicate dietary requirements.

Conservation of Iron in Metabolism

Iron occupies a peculiar position among the inorganic elements essential for life in that it is a "one-way substance." As demonstrated by McCance and Widdowson[20] the body has a remarkable ability to conserve iron that has been absorbed and become a part of its tissues. Almost none is excreted in the urine, and the fecal content is largely the unabsorbed food iron. The amount of iron in the body appears to be regulated by controlled absorption. The smallness of the excretion of iron by the kidney or bowel may be due to the fact that activity of the storage organs keeps plasma iron at a low level.[20] When red blood cells are destroyed by the cells of the reticulo-endothelial system, the iron is split off from the pigment fraction of the broken-down hemoglobin and retained by the body to be used again in the manufacture of new hemoglobin by the young red blood cells of the bone-marrow. Similarly, the iron of tissue cells throughout the body is used over and over again.[17] Very little is lost. Accordingly, in the absence of pregnancy, lactation, and blood loss from menstruation or other causes, there is little need on the part of the body for more iron.

Little is known about the factors that influence the storage of available iron in liver, spleen, and bone-marrow. These stores are greatly increased in conditions associated with increased blood destruction, such as pernicious anemia or hemolytic icterus. The tissue iron is tremendously increased also in hemochromatosis, in which disease there is a peculiar disorder of iron metabolism with abnormal deposition of iron to a harmful degree; the amount found in the liver may be several times that usually contained in the whole body, and increased amounts are found in all tissues; there is no evidence of increased blood destruction but at least early in the disease, there would appear to be little restriction on the absorption of iron. In healthy people, on the other hand, absorption of iron seems to occur only in case of need; it has been demonstrated repeatedly that ingestion of a diet rich in iron, with or without administration of iron salts, may fail to give rise to any retention. When there is an experimental (or clinical) iron-deficiency anemia, however, a considerable proportion of ingested iron is absorbed and either utilized in the manufacture of hemoglobin or stored. The factors that limit the absorption when a given amount is stored are unknown. It may be that in some individuals this regulation proves to be defective and the amount stored so small that their ability to withstand appreciable loss of iron is reduced.

Loss of iron from the body, leading to the depletion of iron stores and to varying degrees of iron deficiency, may occur, as noted above, in females during pregnancy, lactation, and menstruation and in males and females as a result of any hemorrhage of sufficient magnitude. The maternal loss of iron during pregnancy and parturition has been estimated variously as from three hundred to six hundred milligrams, the loss of iron in lactation at a little less than one milligram per day, and the loss in menstruation, with great individual variation, at about three hundred milligrams per year. The magnitude of the loss in hemorrhage varies, of course, with the amount and hemoglobin content of the blood lost: one hundred cubic centimeters of normal blood contains almost fifty milligrams of iron.

Supply of Iron

The adequacy of the iron supply of newborn infants depends in part at least on the condition of the mother. If she has suffered from iron deficiency during the later months of pregnancy, the iron stores of the fetus will probably be deficient and although the infant's hemoglobin level may be normal at birth a hypochromic anemia is likely to appear after the third month. Such an anemia may be prevented by treating the mother during pregnancy or by administering iron to the infant at an early date.[4]

After about the sixth month of life the diet must supply the amount of iron required for growth and for the development and maintenance of adequate iron stores. As long as there is need, and probably whenever the iron stores are low, a definite though small proportion of the food iron will be absorbed from the upper intestinal tract. The actual needs would be met relatively easily if all the iron in the food could be absorbed. Only a portion of the iron taken with food is utilized, however; the greater part is excreted, largely unchanged, in the stool. It has often been claimed that certain portions, such as that bound organically in the form of hematin, cannot be utilized at all. Even when soluble inorganic salts of iron are administered only a small proportion is absorbed.

Much light has been shed on this problem in recent years, especially by Whipple and his associates[3, 15, 16, 34] who have shown that iron-deficient subjects will absorb a relatively large proportion of food iron—

up to almost 50 per cent—when the intake is low; with ingestion of larger amounts the proportion falls off sharply, but the actual amount utilized may be considerably increased: when there is no need for the element and the body stores are adequate the absorption becomes negligible. It would appear, moreover, that it is the reserve store of iron in the body, rather than anemia per se, that controls absorption, and that this control is exerted upon the gastrointestinal mucosa which can refuse or accept iron under various conditions. In the light of such experimental work many of the long-accepted ideas about iron metabolism must be reconsidered.

In any case a large excess of iron must be taken in the diet in order to supply the body's requirements for growth and physiologic losses. A safe estimate is to supply from foods of good quality the daily allowance of iron recommended by the Food and Nutrition Board of the National Research Council,[24] as indicated in Appendix Table A. Actually the ingestion of a diet adequate for nutrition with respect to other factors will meet this standard and ensure an intake of iron adequate for virtually all physiologic states in normal people.

The iron content of a number of commoner foods relatively rich in iron is indicated in Appendix Table C, and a complete tabulation in Table B. It should be noted that milk contains very little iron, not more than 0.05 to 0.1 mg. per 100 c.c.; that, with the exception of peas and beans and the green leaves of plants, the iron content of fresh fruits and vegetables is also low; and that the most abundant sources of iron are meats and eggs, the iron content of liver, heart, and kidney being particularly high.

To ensure an intake that is more than adequate, infants may be given cereals enriched with added iron; the early addition to their diet of egg yolk and scraped beef is also recommended. Particular care should be taken that adolescent girls have a suitable diet. As pointed out by Allbutt: "Perhaps every girl, as it were, passes through the outer court of chlorosis in her progress from youth to maturity," a statement more pertinent in his day than now, but still indicating the need for an abundant intake of iron which will be supplied if a diet adequate in other respects is taken at this period of rapid growth and beginning menstruation. The diets of pregnant and lactating women and of all persons suffering even small, repeated hemorrhages should be watched with equal care. The requirement suggested for adult men, on the other hand, is probably higher than necessary, for it has been shown that healthy men may live for months on a very low iron intake without showing a negative iron balance and with no obvious ill effects. Their needs for iron will be abundantly met and their iron stores filled to capacity by an ordinarily adequate diet.

Other factors than the amount of iron in foodstuffs also demand consideration. These include the presence of fatigue, infection, nausea and vomiting in pregnancy, and psychologic influences, all of which may affect the appetite and make it difficult for the patient to take the appropriate foods in adequate quantity. Intestinal disorders such as diarrhea, infections, and steatorrhea may interfere with absorption of iron. The presence of achlorhydria may affect the balance in an adverse direction if there is already a question of deficiency, and perhaps a constitutional variation in the body's regulation of storage and absorption of iron may leave some patients with inadequate stores and a tendency to suffer iron deficiency under strain of blood or other iron loss.

When, in any patient, an iron deficiency has been allowed to develop and hypochromic anemia has resulted, adequate treatment is achieved only by the administration of inorganic preparations of iron; ingestion of a diet of highest iron content obtainable in natural foodstuffs is inadequate or far too slow.

It has been pointed out on sound experimental evidence that minute amounts of copper and perhaps of other metals such as zinc, nickel, cobalt, and manganese may be necessary for hemoglobin formation. The supply of these, however, is adequate in any ordinary diet and presents no clinical problem (see Chapter 14, p. 396).

PATHOLOGIC CHANGES IN IRON MALNUTRITION

The common pathologic changes in iron deficiency have to do with the bone-marrow and circulating blood. With mild deficiency there are no characteristic findings. In cases of moderate to severe anemia the bone-marrow is hyperplastic, the red marrow extending to some extent into the shafts of the long bones; there is a predominance of fairly mature normoblasts with relatively few younger forms.[6] The white cells and megakaryocytes show no distinctive changes. Active in the attempt to repair the anemia, but lacking iron to make enough hemoglobin to fill a normal number of red blood cells, the bone-marrow produces mature red blood cells of varying size, the great majority being thin, small in diameter, and with greatly reduced content of hemoglobin, thus giving a hypochromic microcytic anemia with a low color index. The white blood cells of the peripheral blood have a normal appearance and the actual count is normal or somewhat reduced. The blood platelets are normal or increased in most cases; with severe anemia, they may be reduced.

When the anemia is severe, and particularly in long-standing cases, the spleen frequently becomes enlarged and the heart may be dilated; the nails may become thin, brittle, and scaphoid; the mucous membranes of the tongue and pharynx tend to become smooth and atrophic, while fissures may appear at the corners of the mouth[7] similar to those in IX*c* and *f*, p. 89. The atrophy of the epithelium of the pharynx may be associated with folds or webs of the mucous membrane which, usually situated at the upper end, may cause difficulty in swallowing. Suzman[32] reported one such case in which death resulted from mediastinitis following traumatic rupture of the esophagus; the epithelium of the tongue and esophagus was very thin and showed marked keratinization; there was some submucous lymphocytic infiltration. Whether the changes in the fingernails, tongue, and pharynx are directly due to a prolonged iron deficiency or result from some secondary change, they do appear to be characteristic of the condition and, like the abnormalities of the bone-marrow and peripheral blood, they revert to normal soon after the institution of adequate iron therapy; the spleen also shrinks under such treatment, and the heart becomes normal in size. Atrophy of the mucous membrane of the stomach has also been reported.

THE CLINICAL SYNDROME OF IRON DEFICIENCY

As already stated, the development of a hypochromic anemia is the most prominent and often the only distinctive manifestation of iron deficiency. The associated clinical syndrome is influenced by the primary factors leading to the deficiency and by associated conditions. Because the anemia may appear at different ages and be associated with various states and complications, a number of names have been used to designate what at first appeared to be different syndromes. Thus, in infancy and childhood iron-deficiency anemia has been called by such synonyms as dietary anemia, nutritional anemia, milk anemia, chlorotic anemia, and secondary anemia. The term secondary anemia has unfortunately been used to refer to almost all types of anemia other than pernicious anemia which was so long regarded as the chief primary anemia. It has often been used, however, with special reference to hypochromic anemia, thus leading to confusion of thought and therapy. It would be helpful if both terms—primary and secondary—were dropped completely.

For generations the name chlorosis was applied to the iron-deficiency anemia of adolescence, although the green color of the skin was often lacking even in the days when hypochromic anemia of all grades of severity was common in teen-age girls. This same type of anemia in adult women has of late been given much consideration and such names as idiopathic hypochromic anemia, primary or simple achlorhydric anemia, anemia with dysphagia, chronic chlorosis, and various combinations of these and other names emphasizing a particular associated symptom have been used. When patients with such anemia have become pregnant, and the anemia accordingly more severe, it has been customary to refer to it as anemia of pregnancy. When, as often happens, the anemia first has become manifested in marked degree in middle age, usually after years of menstruation and pregnancies, it has sometimes been called anemia of the menopause. In all groups so far mentioned there is reason to suspect an underlying constitutional factor, often associated with hypochlorhydria or achlorhydria, a defect in the ability to absorb and store iron well, superimposed on which any factors causing material loss of iron or failure to supply iron in the diet will lead to deficiency and anemia.

In men and in most older women a similar hypochromic anemia is produced only by hemorrhage of sufficient magnitude to exhaust normal iron stores.

In the following account, a brief description of the various types of iron-deficiency anemia will be given under the headings as indicated below. A more detailed account will be concerned with the syndrome as it occurs in adult women. It is understood, of course, that the distinctive anemia manifestations are the same throughout.

HYPOCHROMIC ANEMIA

CLASSIFICATION

Hypochromic anemia of infancy and childhood (affects girls and boys).

Chlorosis: hypochromic anemia of adolescence (almost entirely confined to females).

Hypochromic anemia of adult women ("idiopathic").

Hypochromic anemia of pregnancy (largely cases of hypochromic anemia of adult women aggravated by pregnancy).

Hypochromic anemia of severe, chronic blood loss (may affect males or females at any age. Hypochromic anemia in males should always be considered as due to blood loss, and in all instances of hypochromic anemia in females at any age blood loss should be searched for as a possible etiologic factor.)

Hypochromic Anemia of Infancy and Childhood

Iron-deficiency anemia may occur in infancy when the fetal storage of iron has been inadequate because of a maternal deficiency or premature birth. The importance of an abundant initial supply is evident in view of the low iron content of milk and the increasing demands for growth. Even when the initial storage is adequate, deficiency may occur if the administration of iron-containing foods is delayed or insufficient. When the supply proves inadequate a hypochromic anemia develops, which is manifested by varying degrees of pallor, fatigue, weakness, lack of appetite, and the irritability associated with debility. The heart may be dilated and blowing systolic murmurs heard over the precordium; the spleen and liver may become enlarged. Should severe anemia persist long, growth and development may be delayed. A typical hypochromic blood picture is found, the severity of the anemia varying with the degree of iron deficiency. There may be achlorhydria. In the absence of infection or other nutritional deficiencies or retarding influence, patients respond well to administration of inorganic salts of iron such as ferrous sulphate, 0.32–0.65 Gm. (5–10 gr.) per day.

During childhood hypochromic anemia may develop if, for any reason, a diet low in iron is taken for long periods: conversely, a diet adequate in other respects for the needs of the growing child will usually protect against iron deficiency in the absence of material blood loss.

CHLOROSIS: HYPOCHROMIC ANEMIA OF ADOLESCENT GIRLS AND YOUNG WOMEN

Although typical chlorosis with a greenish pallor of the skin is now seldom seen, mild hypochromic anemia is fairly common in adolescent girls and especially in those who, from bad habits of eating, have taken little meat and eggs, or in those who have been subject to severe menorrhagia. Sometimes the pallor usually associated with an anemia of mild or moderate severity is obscured by the flush of youth. The clinical picture, modified by the reactions of a rapidly maturing young woman, is essentially the same as that to be described under hypochromic anemia of women.

HYPOCHROMIC ANEMIA OF ADULT WOMEN (IDIOPATHIC HYPOCHROMIC ANEMIA)

The frequent occurrence and recurrence of hypochromic microcytic anemia in women between puberty and the menopause has been the subject of many reports[9, 10, 18, 35, 36, 37] in the last twenty years. The patients affected may have suffered anemia in adolescence; it tends to recur or be aggravated during pregnancies; it may be first recognized at the menopause. The very frequent association of achlorhydria has naturally suggested that there is some defect in absorption or, on the other hand, that the achlorhydria is a manifestation of a constitutional type of which an anomaly in iron metabolism is another feature. It is common experience that these patients are nervous, anxious people; certainly symptoms referable to disturbance in function of the cardiovascular and gastrointestinal systems are of frequent occurrence and often modify the clinical picture. Whether such symptoms are manifestations of a special constitutional tendency and are therefore more common in women with a chronic hypochromic anemia than in women suffering ill health from other causes is difficult to determine. Their presence is an indication for the type of psychotherapy that gives explanation, assurance, confidence, and encouragement to the patient: such therapy may lead to remarkable improvement and relief of symptoms that may otherwise persist after the hemoglobin has risen to normal levels under specific iron therapy. There is, in any case, reason to believe that a proportion of women (perhaps 10 to 15 per cent or more) have a constitutional anomaly of iron metabolism, as a result of which they may be unable to withstand the losses associated with increased menstrual flow, pregnancy, and lactation. The resulting anemia is commoner among poor people. Its natural course is one of gradual onset and great chronicity, with a strong tendency to recur after relief on temporary iron therapy. Unfavorable social and economic factors often aggravate the situation by making it difficult for the patient to obtain or eat an adequate diet and by increasing nervous symptoms.

It is often difficult to determine the date of onset. Usually there is a history of slowly increasing weakness and fatigue, but these symptoms may come on so gradually that they have been accepted by the patient as the normal state of affairs and hardly noticed; they may appear as part of a gradual transition over a period of years, in which time there may have been several striking incidents such as pregnancies, acute illness, or social and domestic changes. More notable symptoms are often delayed till the anemia has become severe. There may or may not have been a history of menorrhagia or other blood loss, but a history of menorrhagia is common. Sometimes there is a history of peculiarly bad dietary habits, as in the case of a 26-year-old married woman with a hemoglobin of 7.5 Gm. per 100 cc. and red blood cell count of 5,000,000, who had never in her life eaten any flesh whatsoever, not even during her nurse's training. More frequently the patient has eaten poorly—sometimes a diet of toast, tea, and milk—and has been thin and tired for years; on the other hand, obesity is not uncommon; and, again, the diet may appear to have been normal.

With progression of the anemia a generalized pallor is noted. One of the earlier symptoms is shortness of breath on exertion; this becomes gradually more marked if the anemia becomes severe. It is commonly associated with palpitation and tachycardia and with a pounding pulsation in the head that may be distressing. The patient may complain of dull, persistent headache. Syncopal attacks occur but are relatively infrequent. If the appetite was not already poor, it usually fails and often becomes capricious. Mild epigastric discomfort and bloating, aggravated by meals, and constipation are common. Evidence of emotional instability may precede development of the anemia and be aggravated by it, or may appear as the disease progresses; apathy and lassitude are frequent symptoms, as are increased anxiety and irritability. These patients often complain of neuralgic pains in various parts of the body and, in particular, of dull pain under the left breast. Paresthesias involving the hands and arms and, less commonly, the feet may come as a late symptom, but the paresthesias are not so definite and persistent as in pernicious anemia, and seldom are a striking cause for complaint. In cases of long standing the patient may complain of mild soreness of the tongue and of difficulty in swallowing; because the latter symptom is aggravated by apprehension and tension, it has often been wrongly considered as purely a nervous manifestation. Menorrhagia is a frequent early symptom: it may change to amenorrhea. Even when the anemia is severe and of long duration fertility does not appear to be affected: many of these patients, untreated, have had repeated pregnancies. In some of the older patients with damaged coronary arteries, effort gives rise to definite angina which disappears, often for years, on adequate therapy. Some patients are able to carry on remarkably well in ordinary or slightly restricted activity in spite of fatigue, weakness, and other associated symptoms until the hemoglobin has fallen to very low levels (6 to 3 Gm. per 100 cc.).

EXAMINATION

The patient is often a worn, tired, thin woman, looking older than her years, with a wrinkled face and a sallow pallor. Occasionally, especially in younger, well-nourished subjects, the patient has not entirely lost the bloom of youth and the pallor may be hidden by a deceptive malar flush. In all severe cases, however, the pallor becomes marked; it affects the skin of the face and hands and of all parts of the body that normally present a good color, as well as the mucous membranes of the lips and conjunctivae, and in these ways can usually be distinguished from the pallor associated with fatigue and ill health in the absence of anemia. In long-standing cases there is often a light brown pigmentation on the lips and cheeks which may be either diffuse or blotchy. Sometimes the face is pale, white, and puffy but more commonly thin, wrinkled, and sallow. The skin may be thin and dry or a little scaly, and fissures may appear at the corners of the mouth.[7] The pupils are often dilated and the sclerae may appear to be bluish. A jaundiced tint is not seen.

The tongue is usually clean, pale, often small, and there may be atrophy of the papillae, first at the sides and then over the surface. Sometimes, especially in women with false teeth, the tongue is large and flabby.

The fingernails are normal in appearance until moderate to severe anemia has been present for a long time; then they tend to become thin and brittle and ultimately may be grossly scaphoid, each able to hold a drop or two of water without overflowing (see Fig. 13).

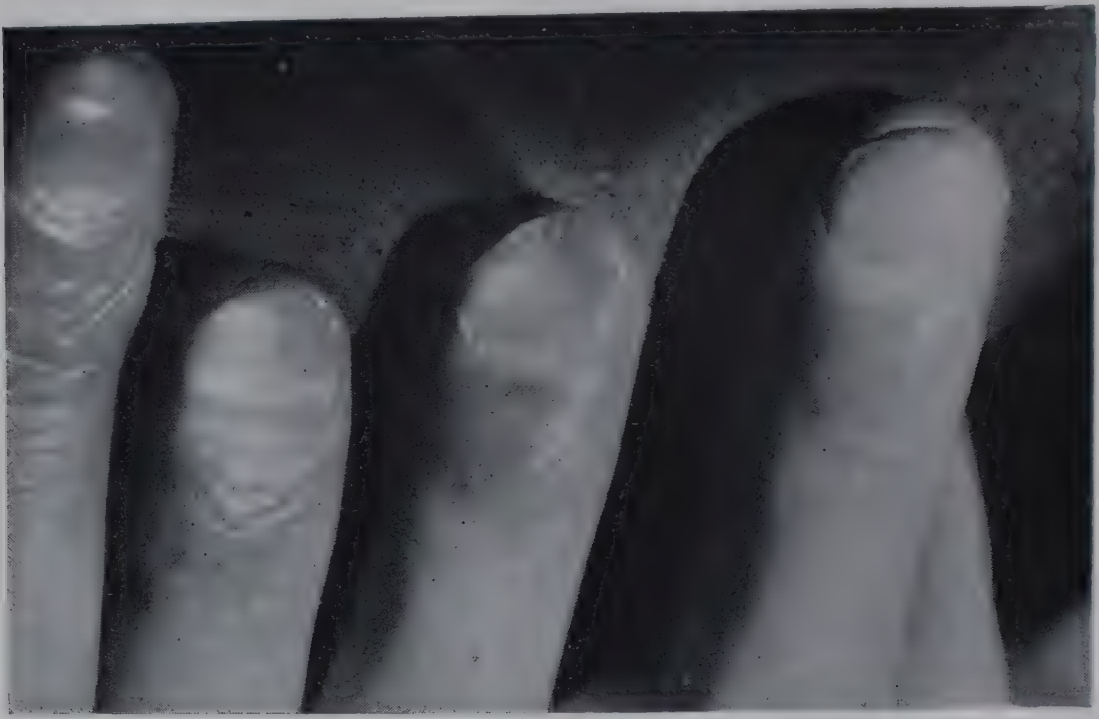

FIG. 13. Scaphoid, thin, brittle fingernails (koilonychia) of patient with hypochromic anemia and other manifestations of severe iron deficiency. (*Picture taken by Dr. J. A. Dauphinee.*)

CASE REPORT FOR FIG. 13

A 26-year-old woman had had poor health (tiredness and shortness of breath) almost constantly since marriage at 18 years of age. She had five pregnancies (1939, 1940, 1942, 1943, and 1945) during which she was much troubled with vomiting, and between which she never regained her strength and energy. For one year before admission to the Toronto General Hospital on April 26, 1946, she was troubled with mild dysphagia; for five months she suffered soreness and fissures of the vulva and also at the angles of the mouth. She had not menstruated since December, 1945. The diet was not grossly deficient but the appetite was poor. She was a thin, pale, tired woman with brown pigmentation of the face, looking much older than 26 years. There was atrophy of skin with fissures at angles of the mouth, the mucous membrane of tongue was smooth and thin, and there was marked koilonychia (Fig. 13); systolic murmurs over the precordium, and an impalpable spleen. Haemoglobin was 4.0 Gm. per 100 cc.; R.B.C. 2,600,000; color index 0.5. Blood smear was characteristic of severe hypochromic anemia.

She responded well in every way to iron therapy and the hospital regimen.

In patients with severe anemia the heart may sometimes be dilated, the enlargement being recognizable clinically as well as by radiologic examination; more commonly it is not possible to demonstrate any increase in size. In almost all cases, however, by the time the hemoglobin has fallen as low as 7 Gm. per 100 cc., blowing systolic murmurs are heard over the precordium; they are often loudest in the pulmonary area but sometimes in the mitral area. In severe anemia a humming murmur also is heard over the veins of the neck and, when the hemoglobin has fallen to about 5 Gm. per 100 cc. or lower, a long blowing murmur is heard on auscultation over the eyeball and sometimes over the skull. All these murmurs disappear when the hemoglobin rises on iron therapy. Definite signs of passive congestive failure are seldom found. Edema of the ankles and feet may be present, however, and the liver is often slightly enlarged. The blood pressure is usually normal or slightly reduced.

Some enlargement of the spleen is the rule in cases with chronic severe anemia; it is then easily palpable, firm, and not tender.

The temperature is usually normal till the hemoglobin has fallen to low levels, when mild fever is common; seldom does the temperature rise above 100° or 101° F., however; the afternoon peak usually lies between 99° and 100°. The occurrence of anemia, fever, and splenomegaly with cardiac murmurs has led occasionally to an erroneous diagnosis of bacterial endocarditis.

The *blood picture*, like other manifestations of the disorder, varies with the degree of iron deficiency. At first there is a slight reduction in hemoglobin, while the red blood cell count remains normal. At this stage the red blood cells are normal in appearance and it is not possible to make the diagnosis by examination of the smear alone. When the supply of iron becomes so insufficient that the hemoglobin is decreased to about 9 Gm. per 100 cc., one begins to see the characteristic smaller, pale cells; this change becomes more marked as the anemia becomes more severe. In extreme deficiency the hemoglobin may fall as low as 3 Gm. and the cells become so thin and pale that a color index as low as 0.4 may be obtained. More commonly each cell contains about half the normal amount of hemoglobin so that, in chronic severe cases when the hemoglobin ranges from 3 to 6 Gm., the corresponding red blood cell counts will vary between 2,000,000 and 4,000,000. At this stage the red cells vary considerably in size; the great majority are smaller than normal but a few large cells and some very small or deformed cells are seen; all are thin and pale. In untreated cases one never sees the big, thick, deeply stained cells that are so characteristic of pernicious anemia. There is a slight increase in reticulocytes.

The white blood cell count usually varies within normal limits. In severe anemia, however, the white cell count may fall to 3000 or 2000. Even with such a leukopenia the differential count is usually normal, although the polymorphonuclear neutrophiles may be slightly reduced.

The platelets are normal or slightly increased until the anemia becomes extreme, when they may be reduced.

In this and other types of chronic iron-deficiency anemia a remarkable change takes place on institution of iron therapy. Beginning toward the end of the reticulocyte response, which occurs in the first two weeks and usually is not as great as in cases of pernicious anemia with anemia of equal severity, large, well-filled cells begin to be seen among the pale, thin cells of the blood smear. They increase rapidly in number till by the third week they dominate the picture. The smear might then be wrongly diagnosed as one of pernicious anemia (if one did not know any details of treatment) but for the presence of a small number of the thin, pale cells characteristic of iron deficiency. A few weeks later the blood picture has become essentially normal (see Fig. 14).

Case Report for Fig. 14

Since 1940, this 62-year-old woman had suffered increasing pallor, fatigue, shortness of breath, and loss of weight. She had no abdominal pain at any time and was admitted in March, 1942, for investigation of anemia (Fig. 14). Hemoglobin was 3.2 Gm. per 100 cc.; R.B.C. 2,700,000. She was treated with iron, without transfusion, and had an excellent response. Because of the typical picture of hypochromic anemia in a 62-year-old woman a gastric series was then done in search for a bleeding lesion; a large polypoid carcinoma of the stomach was demonstrated; a gastrectomy was done, and she was well when last heard from in May, 1947.

OTHER LABORATORY FINDINGS

In the absence of complications, examination of the urine shows nothing abnormal; it is pale in comparison with the highly colored urine of hemolytic anemias. The blood-sedimentation rate is less reduced than is usually found in other types of anemia of equal severity, and often is normal in patients with mild to moderate grades of anemia. The serum bilirubin is normal or diminished (van den Bergh less than 0.3 mg.; icterus index less than 4). A large proportion of patients have an achlorhydria or marked hypochlorhydria persisting after injection of histamine.

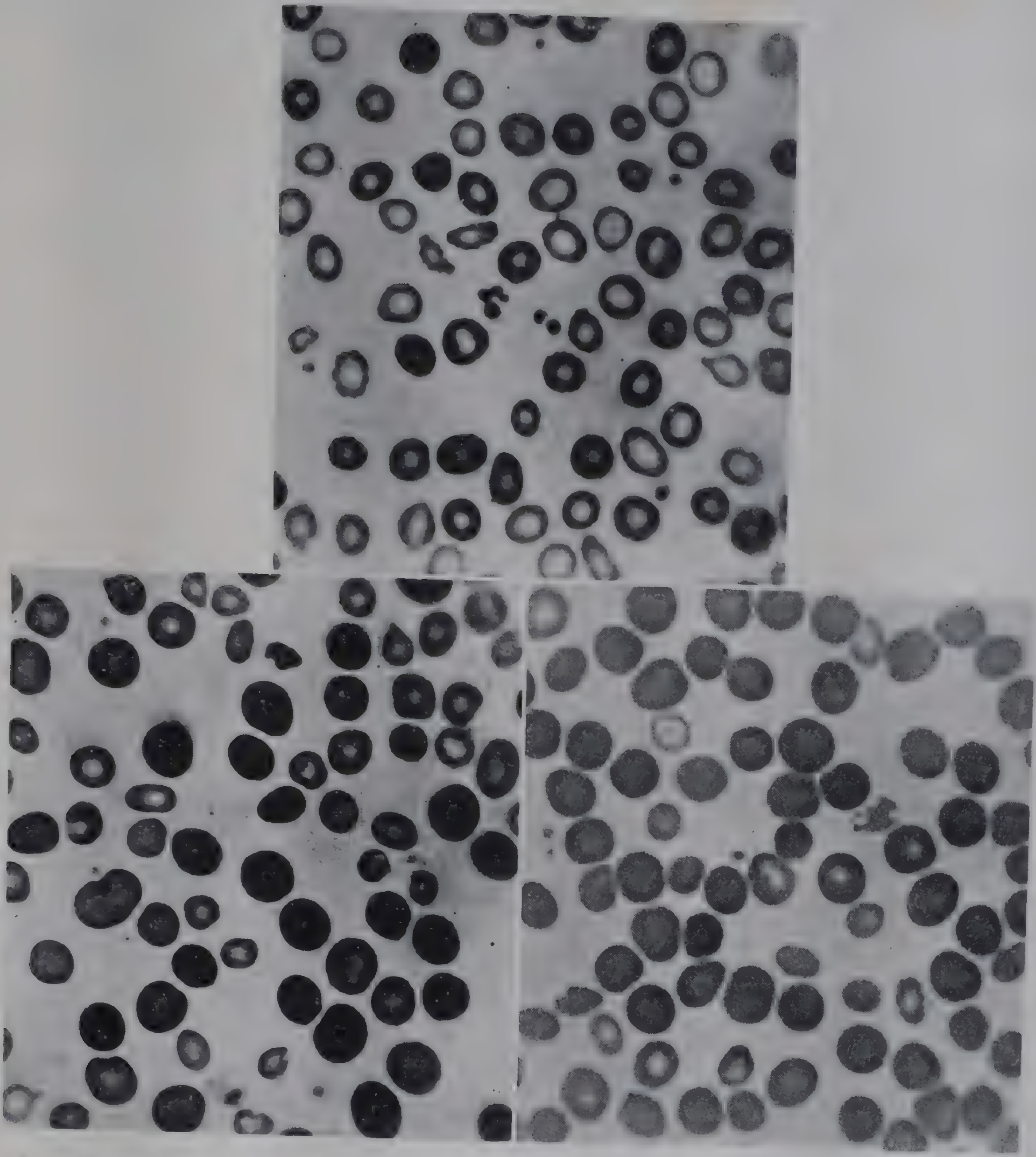

FIG. 14. Initial blood film and early changes on iron therapy (× 1000). *Top:* Initial film. Hb. 4.0 Gm.; R.B.C., 2,700,000; C.I., 0.4. Presents the typical picture of a hypochromic microcytic anemia. One may note the general hypochromia, the preponderance of small cells, and the presence of numerous platelets. *Bottom left:* Blood film after fourteen days on iron therapy. Hb. 5.6 Gm.; R.B.C.; 3,000,000; C.I., 0.6. Note the marked increase in large, fairly well filled cells and the persistence of numerous small hypochromic cells. On careless examination, the smear at this stage might be mistaken for pernicious anemia. *Bottom right:* Blood film taken on twenty-first day of therapy. Hb., 6.8 Gm.; R.B.C., 3,200,000; C.I., 0.7. There is less variation in size, fewer small pale cells, and fewer large cells. A few weeks later the smear had a normal appearance.

Hypochromic Anemia of Pregnancy

It is well known that, associated with the increase in blood volume of later pregnancy, there is a mild reduction in the hemoglobin level and in the red cell count—a physiologic anemia. Pregnant women with a pre-existing tendency to suffer from iron deficiency are likely to be the subjects of a more severe anemia of hypochromic type. The transference to the fetus of an amount of iron equivalent to 500 to 1000 cc. of normal blood places a strain on the already deficient stores. Many of these patients are tired, nervous, and overworked and, especially if there is much vomiting, their diet is likely to be inadequate in quantity and quality and poor in iron at a time when iron is badly needed. Sometimes the anemia is first recognized in late pregnancy. In any case it appears to be an aggravation of an idiopathic iron deficiency. The symptoms and signs differ only in so far as they are modified by manifestations of pregnancy. The blood picture shows no distinctive features.

This hypochromic anemia of pregnant women must be differentiated from the less common and usually more serious macrocytic anemia sometimes found during pregnancy.

Hypochromic Anemia of Severe, Chronic Blood Loss

Immediately after a single large hemorrhage in previously healthy people, the hemoglobin and red blood cells are reduced to an equivalent degree; the red cells are normal in appearance; there is an early, rather transient leukocytosis and increase of blood platelets. In the absence of complicating conditions, such as infection, a reticulocyte response occurs and the hemoglobin and red blood cell count rise quickly and spontaneously to normal. A hypochromic anemia appears only if the hemorrhage is large enough to exhaust the iron stores normally available for new hemoglobin formation. It is important to remember that the iron stores of healthy people are usually able to withstand the strain of more than one large hemorrhage or of fairly prolonged, chronic, or recurrent bleeding; this has been well demonstrated in professional blood donors. The nature of the onset of hypochromic anemia of blood loss depends on the rate and magnitude of the hemorrrhage. When the stores are rapidly depleted by large hemorrhages, the hemoglobin and red blood cell count fail to rise to normal levels without administration of inorganic iron, and a hypochromic picture develops; the red cells change gradually over a period of a few weeks, well-filled, normal cells being replaced by thin, pale, smaller cells. If the hemorrhage is slight and chronic or recurrent, the anemia will develop much more slowly. But the ultimate clinical and hematologic pictures will be those of hypochromic iron-deficiency anemia superimposed on symptoms of the disease giving rise to the hemorrhage. Obviously the clinical picture will be almost identical in those patients suffering prolonged, mild, persistent or recurrent bleeding with few symptoms.

Usually the site of the hemorrhage is known and the etiologic lesion either obvious or recognized without difficulty. Sometimes, however, a hypochromic anemia provides the first evidence of a bleeding lesion which may even be quite symptomless; such may be the case, for instance, in patients with ulcers associated with hiatus hernia, or carcinoma of the stomach or of the cecum (see Fig. 14 and case report).

The blood picture in hypochromic anemia of hemorrhage is the same as in other types of hypochromic anemia. Achlorhydria is, however, much less common except when the primary lesion is a carcinoma of the stomach.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of iron malnutrition is easy when the deficiency is severe. In no other anemia do the red cells contain so little hemoglobin; in none other does one find a color index as low as 0.5, or the cells so thin and pale. Accordingly, in severe cases the diagnosis can be made with certainty on the blood findings alone, and there is no difficulty provided one can depend on the accuracy of the blood examination. The diagnosis is just about as certain on clinical grounds when, in addition to an obvious anemia, the patient presents the characteristic thin, brittle, spoon-shaped nails with or without atrophy of the tongue, fissures at the corners of the mouth, brownish pigmentation of the skin of the face, or dysphagia. In either case the diagnosis is made with ease and confirmed by the response to therapy with iron.

If the anemia be of slight degree, on the other hand, there are few clinical symptoms and no distinctive signs. A history of previous attacks, or of menorrhagia, or of prolonged poor diet may suggest the possibility of iron deficiency and direct attention to the blood examination. But the early hematologic findings are also far from being distinctive. When the hemoglobin is only slightly reduced and the red blood cell count normal, it is quite impossible to have a very low color index, and the appearance of the red blood cells is not materially different from that often found in healthy people or in patients with a mild anemia secondary to factors that depress the bone-marrow. Until the hemoglobin falls to around 8 or 9 Gm. per 100 cc. or lower, a very low color index cannot be obtained. A patient with a hemoglobin of 9 Gm. per 100 cc. and red blood cell count of 5,000,000 almost certainly has a hypochromic iron-deficiency anemia; but should the red blood cell count be 4,000,000 one might not be able, without a test of iron therapy, to distinguish between hypochromic anemia and anemia secondary to some other serious disease. It is true, of course, that in most anemias caused by infection, neoplasm, exposure to poisonous chemicals, renal insufficiency, and so forth, the red blood cell count is depressed as much as the hemoglobin, the red cells are normochromic and the color index has a normal range between 0.8 and 1.0; such findings rule out hypochromic anemia. But occasionally anemias secondary to infection or Hodgkin's disease, etc., have a color index as low as 0.7, and then it is difficult to distinguish by the hematologic findings between them and a mild hypochromic anemia. It must be remembered, however, that when such conditions give rise to even a mild anemia there are definite severe symptoms from the primary condition, whereas few patients will have notable symptoms from iron deficiency until the hemoglobin has fallen to much lower levels and even then they are likely to be mild. Sometimes clear differentiation is made only by test of therapy.

The diagnostic value of therapeutic trials depends on whether the patient is in a steady state of chronic anemia and free from factors such as infection that might inhibit the bone-marrow at the beginning of specific iron therapy. Obviously one would not administer iron as a diagnostic test to a patient whose anemia was due to recent hemorrhage and whose hemoglobin might rise spontaneously in any case; nor would one consider it a fair diagnostic trial to give iron to a patient whose anemia might be due to an infection that was subsiding either spontaneously or under chemotherapy. The test would be unsatisfactory also in a patient with iron-deficiency anemia and associated infection until the infection is controlled, for infection might inhibit the bone-marrow and prevent or retard a response to iron. Having regard for these limitations, however, the therapeutic trial of iron alone is a valuable diagnostic aid in mild cases, and gives useful confirmation in all patients with definite hypochromic anemia of greater severity.

From what has been said it is obvious that pernicious anemia will never be confused with iron deficiency if accurate measurements of hemoglobin and red blood cell count are available and a careful examination of satisfactory blood films is made. In cases of incipient pernicious anemia, large cells are often found in the smear before the hemoglobin has fallen; the red blood cell count tends to fall more rapidly than the hemoglobin percentage, and a high color index is usually found at an early stage. In severe cases there will never be any difficulty if the red blood counts are accurate, for at a given low level of hemoglobin the red blood count will be about twice as high in iron deficiency as in pernicious anemia (see Fig. 15).

It should be remembered, however, that pernicious anemia, as well as other serious diseases, may develop in women with preexisting iron deficiency. The iron reserves, inadequate for the manufacture of enough hemoglobin to fill the relatively numerous hypochromic cells, then become quite adequate to provide the smaller amount of hemoglobin required to fill the greatly reduced number of red cells in patients with pernicious anemia. Accordingly, the characteristic hematologic picture of pernicious anemia soon appears and persists until specific liver therapy is given. On injection of potent liver extract there follows a typical reticulocyte response, with rapid rise in the red blood count. The hemoglobin soon lags behind, however, and a picture of iron deficiency develops again as the red cells rise in number, and it persists till relieved by administration of iron. A typical instance is illustrated in Figure 16. Iron deficiency occurs in women with pernicious anemia in about the same incidence as in other women of corresponding age group. It appears in male pernicious-anemia patients under continued liver treatment only when a bleeding lesion has depleted the large iron stores.

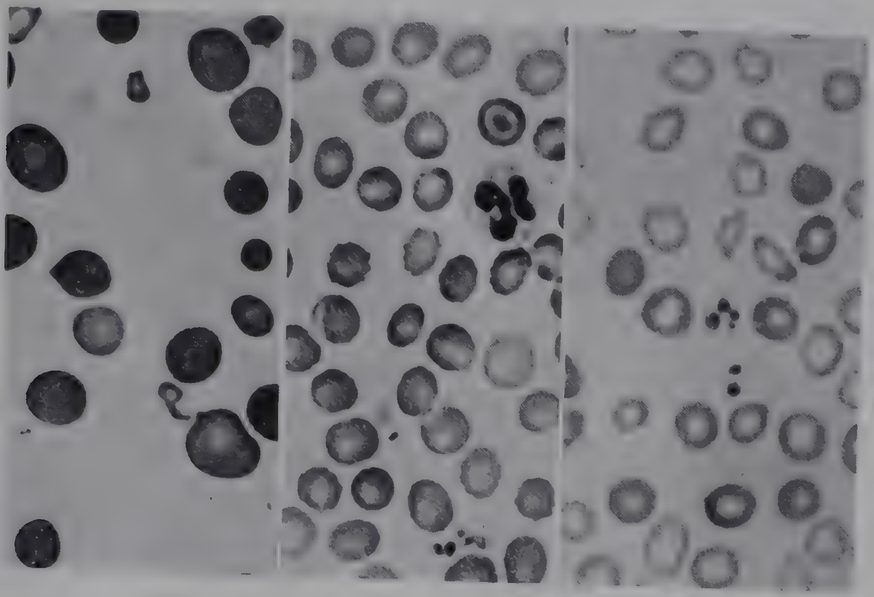

FIG. 15. Comparison of blood films of pernicious anemia, normal and hypochromic iron-deficiency anemia. (× 1000.) *Left:* Patient with pernicious anemia. Hb. 2.3 Gm.; R.B.C. 700,000; C. I. 1.14. *Middle:* Normal patient. Hb. 14.0 Gm.; R.B.C. 5,600,000. *Right:* Patient with severe iron-deficiency anemia. Hb. 3.0 Gm.; R.B.C. 2,700,000; C.I. 0.4.

CASE REPORT FOR FIG. 16

This 34-year-old woman was said to have had anemia in early adult life and had often taken iron. Some eight to ten months before her first admission to the Toronto General Hospital on April 24, 1935, there had been a definite change in her symptoms and she became progressively worse till on admission she presented the typical clinical and hematologic picture of pernicious anemia. Iron had been given with effect for three weeks before she was sent to hospital. Following initiation of regular intramuscular liver therapy on April 24, a reticulocyte reaction began on the third day and reached a peak of 27 per cent on April 30. As shown in the accompanying chart (Fig. 16), the R.B.C. rose in three weeks from an initial level of 700,000 to 3,400,000. The hemoglobin also rose rapidly at first but soon lagged behind the red blood cells and finally

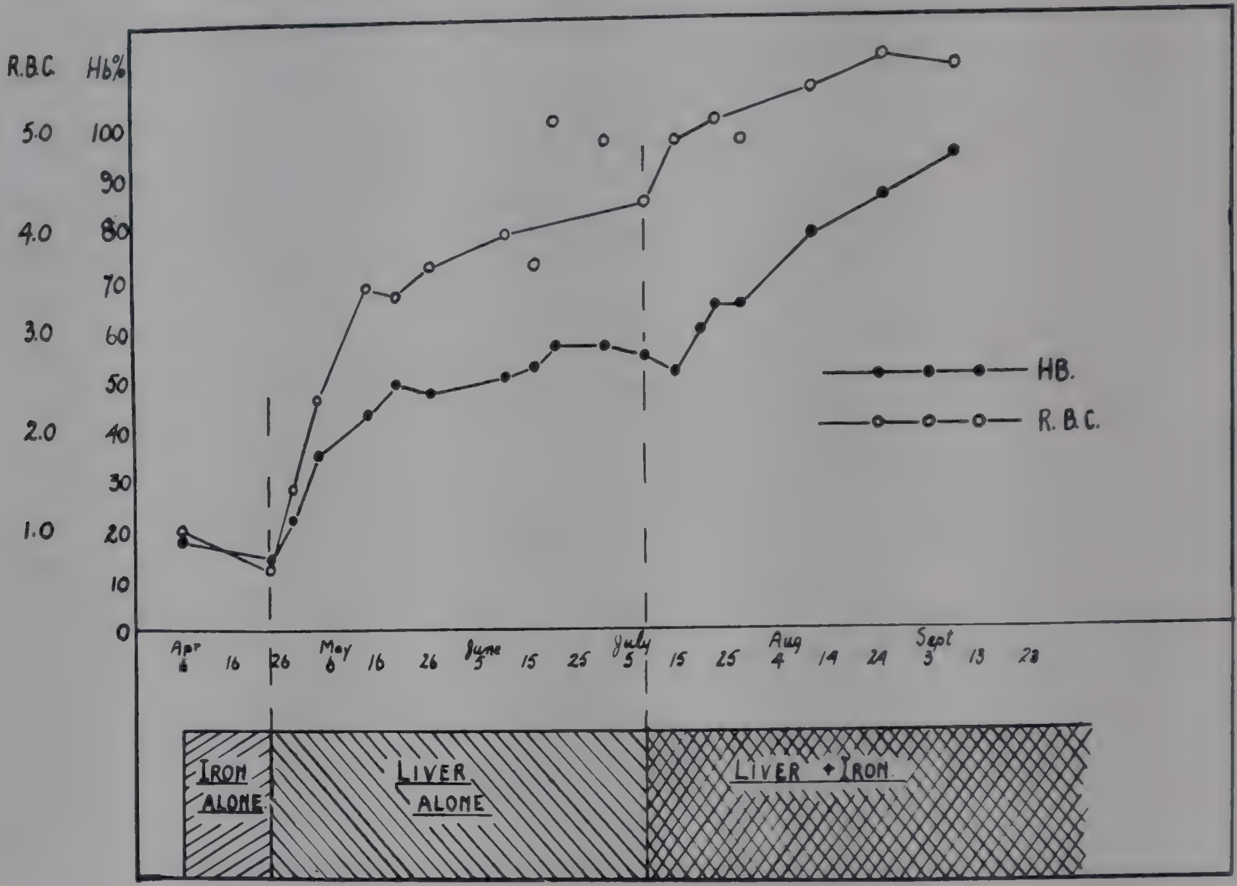

FIG. 16. Pernicious anemia with latent iron deficiency: improvement on liver therapy, with change from hyperchromic to hypochromic state; complete relief of anemia later on addition of iron therapy.

remained nearly stationary at about the 50 per cent level for almost a month, during which time the smear gradually changed till it presented a picture of moderately severe hypochromic anemia. On addition of iron therapy, the hemoglobin began to rise again and the blood picture soon became normal.

In aplastic anemias, from any cause, the red cells are normochromic and the color index is virtually 1.0. Again, if the red blood counts are accurate, the two types of anemia will not be confused.

Iron-deficiency anemia is often wrongly diagnosed when symptoms of chronic ill-health and fatigue, the result of overwork, strain, and worry, are attributed either to a nonexistent anemia or to an anemia too mild to give rise to the presenting symptoms. The patients are often pale and may be sallow. The symptoms disappear on adequate treatment of the primary nervous condition by psychotherapy and institution of a suitable regimen. It is frequently diagnosed in error also when the anemia of patients with subacute or chronic infections, tumor, metabolic diseases, and so forth is considered as being due to iron deficiency. Such anemias usually have a normal color index, and the patient is not helped by iron therapy. In most instances the mistake is due to faulty blood work or an erroneous interpretation of the blood picture. A trial of iron may sometimes be indicated, however, as a diagnostic test.

There is greater difficulty when patients with iron deficiency actually have other diseases. Since the iron deficiency is a chronic condition, other acute and chronic disorders may be associated with it. The complete diagnosis is made by consideration of the whole clinical and hematologic picture; it is simplified when the hypochromic anemia disappears—often slowly—on iron therapy.

Finally, and perhaps most important of all, it is not enough to diagnose the anemia as a hypochromic iron-deficiency anemia and treat it successfully with iron. In men and older women particularly, it is necessary to remember that hemorrhage is almost certainly the primary factor. Accordingly, one must look for the hemorrhagic lesion. While the nature of the primary disease may be obvious, it sometimes happens that a hypochromic anemia is the first manifestation of an almost symptomless carcinoma or other gastrointestinal lesion.

TREATMENT

Adequate treatment of patients suffering from hypochromic iron-deficiency anemia consists in the administration of inorganic salts of iron as specific therapy for the anemia and the institution of general care of the patient with regard to: regulation of rest and activity; ingestion of an adequate diet; symptomatic treatment of any troublesome temporary symptoms; investigation into possible causes of hemorrhage, and treatment of the primary lesion if found; relief of anxiety by adequate sympathetic explanations, and encouragement and alleviation, if possible, of any unfavorable domestic or social conditions. Transfusion is not indicated except when a patient with severe anemia faces a crisis such as labor, an emergency operation, or superimposed hemorrhage. It is safer and easier to relieve the anemia by administration of iron.

In the absence of infection or other retarding influences, the patient will respond well to oral administration of inorganic iron preparations. It is generally accepted that ferrous salts are more readily absorbed than ferric[23] and may, accordingly, be used in smaller dosage. Ferrous sulphate (0.3 Gm. given three times a day with or after meals) is usually effective (see Fig. 17).

Case Report for Fig. 17

This 43-year-old married woman, who had never eaten much meat, had had three pregnancies: one living child, now 18 years of age, and two miscarriages. At 38 years of age she was said to be anemic and was treated with liver but given no iron. She continued to be in rather poor health from this time and in the last two years had had moderate menorrhagia. In the year before admission to hospital she became more tired and more short of breath, suffered from palpitation and complained of anginal pain on severe exertion. Her fingernails became thin and brittle. She was a pale, sallow woman without any icteric tinge, who lay comfortably in bed in no distress. A loud, blowing systolic murmur was heard over the base of the heart; her spleen was easily palpable. Hb. 3.2 Gm. per 100 cc.; R.B.C. 2,400,000. Gastric content contained no free hydrochloric acid even after administration of histamine. She responded well in every way to administration of iron.

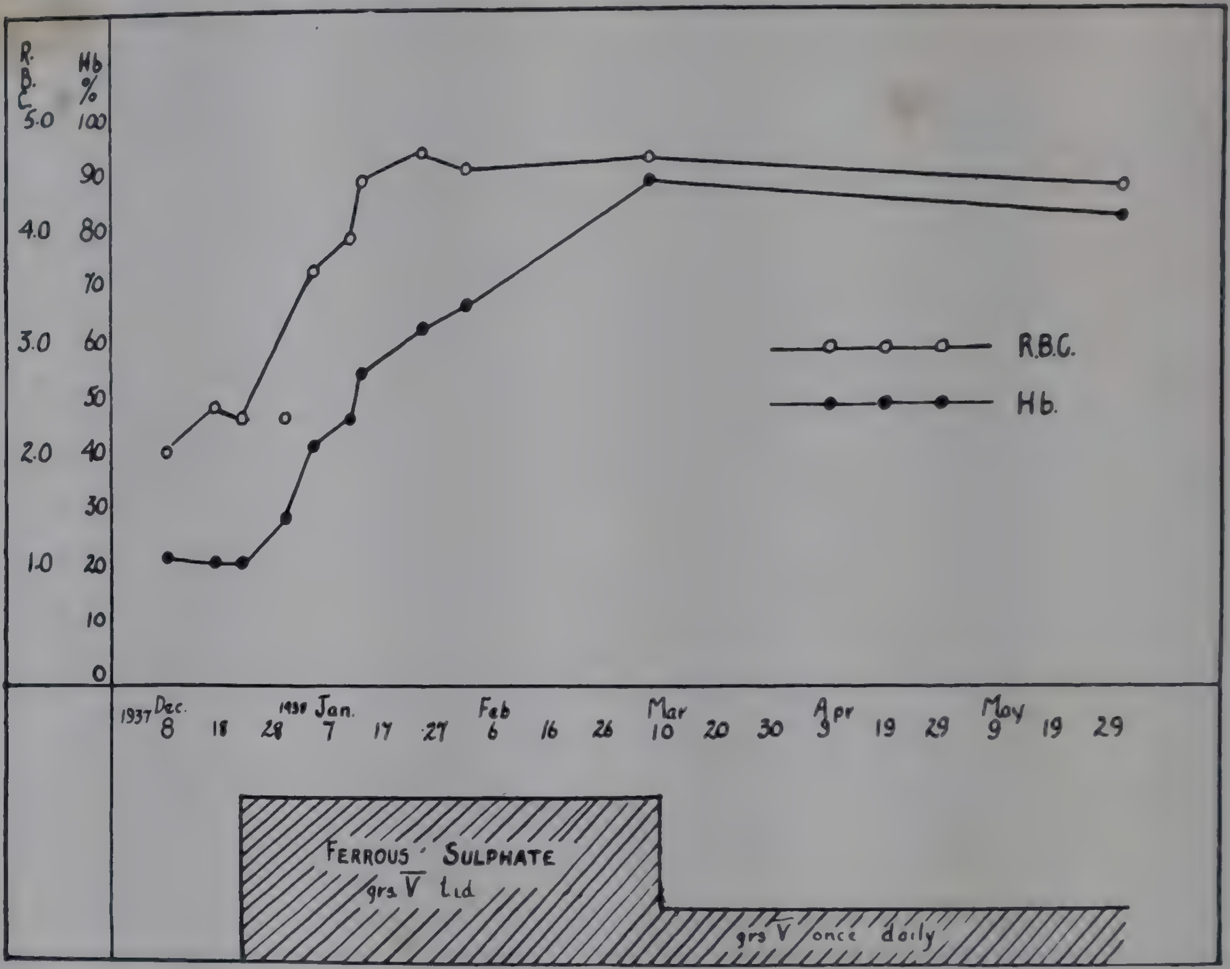

Fig. 17. Idiopathic hypochromic anemia: response of the hemoglobin and red blood cells to administration of iron.

Heath and Patek[18] point out that the following daily dosage of different preparations of iron will provide adequate therapy for the average case: ferrous sulphate, 0.8 Gm.; ferrous carbonate, 0.8 Gm. (a 0.3 Gm. Blaud's pill contains .065 Gm. of ferrous carbonate); iron and ammonium citrate, 6.0 Gm.; reduced iron, 3.0 Gm. It is well known that the optimal dosage varies greatly in different persons. Amounts smaller than those mentioned will be adequate for many men suffering posthemorrhagic iron-deficiency anemia. Patients with idiopathic hypochromic anemia, on the other hand, may sometimes require even larger quantities. Accordingly, whenever a patient is not responding to the therapy as expected, the dosage should be materially increased—doubled or trebled if necessary; one should also search for any complicating infection or other condition that might retard the response to iron.

The hematologic reaction to adequate iron therapy is striking in severe cases. A reticulocyte response begins usually between the third and fifth day and reaches a peak about the tenth day. As pointed out by Minot and Heath,[21] there is an inverse relationship between the height of the reticulocyte peak and the severity of the anemia: when the level of hemoglobin is about 3 Gm. per 100 cc., the reticulocytes usually reach a peak of between 8 and 16 per cent; when the level is about 6 Gm., the peak lies between 4 and 12 per cent; and when the hemoglobin level is around 9 Gm., the peak is between 2 and 6 per cent. After an initial lag of five to ten days and during the reticulocyte reaction, the hemoglobin begins to rise and increases at a rate varying from 0.07 to about 0.3 Gm. per 100 cc. per day. In patients with less severe anemia, with hemoglobin of 8 Gm. or over, the rise per day is slower than in more severe cases. There is a wide variation in the individual response, however, and the effect is sometimes delayed by infection or other noxious influences. It is an old observation also that a good response may not appear till after a period of rest. In some instances the hemoglobin rises rapidly till it reaches a level of about 10 Gm. and then very slowly over a period of weeks or months to the normal level for the individual concerned.

Usually the hemoglobin has risen to normal by the end of the second month of treatment. By this time symptoms directly referable to the anemia have cleared up and the patient is in a state of convalescence. The heart has become smaller and the blowing systolic murmurs have disappeared. The spleen is frequently no longer palpable. Pigmentation of the face and fissures at corners of the mouth are clearing. The tongue has become normal in appearance. In patients with koilonychia, growth of more normal nails has already begun but it requires the usual period of several months for the firm new nail to grow right out. Similarly, dysphagia, if present, has become less troublesome; it gradually disappears (Figs. 18 and 19).

Case Report for Figs. 18 & 19

This 50-year-old woman had never been robust. In adolescence she was troubled with palpitation and shortness of breath on exertion. In her middle thirties she was ill for two years and was said to have had a nervous breakdown. She continued in indifferent health till 48 years of age when menstruation ceased and she began to have hot flushes. She was extremely tired and began to be very short of breath on exertion. For the year before admission to the Toronto General Hospital she found increasing difficulty in swallowing and finally was almost unable to eat any solid food. For six months she suffered angina on slight effort. On admission she was pale, sallow, and looked tired; fingernails were thin, brittle, and scaphoid; the heart was dilated and blowing systolic murmurs could be heard over the whole precordium; the spleen (unusually large) could be felt 7 cm. beyond the left costal margin; hemoglobin was 5.0 Gm.; R.B.C. 4,500,000; blood smear was characteristic of severe iron-deficiency anemia. A barium-paste film of the esophagus, taken on February 11, 1938, by Dr. A. C. Singleton, shows a well-marked constriction at the upper end of the esophagus about one inch below the introitus, presenting the characteristic appearance of a web (Fig. 19). Direct esophageal examina-

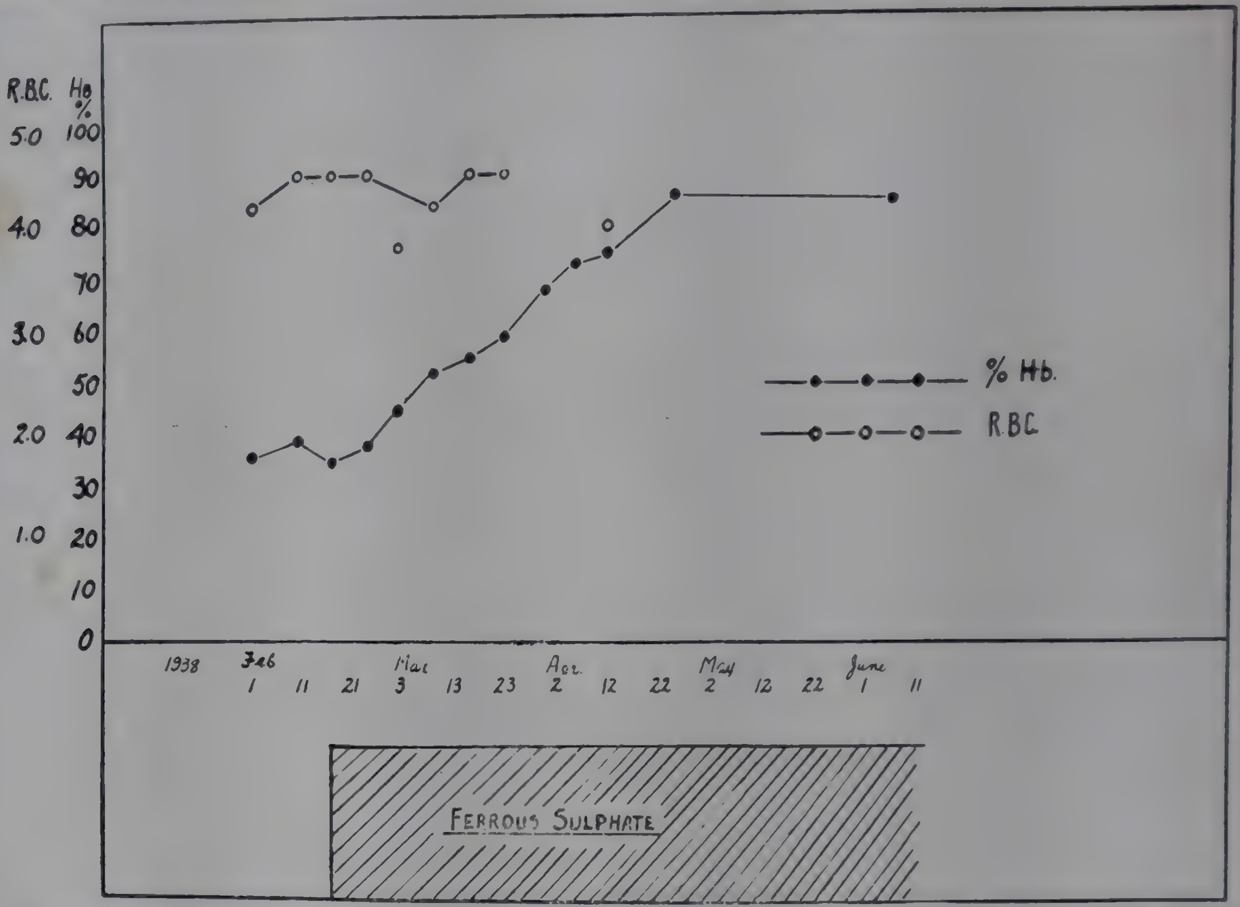

Fig. 18. Iron-deficiency anemia with marked dysphagia and koilonychia. Response of hemoglobin and red blood cells to administration of iron.

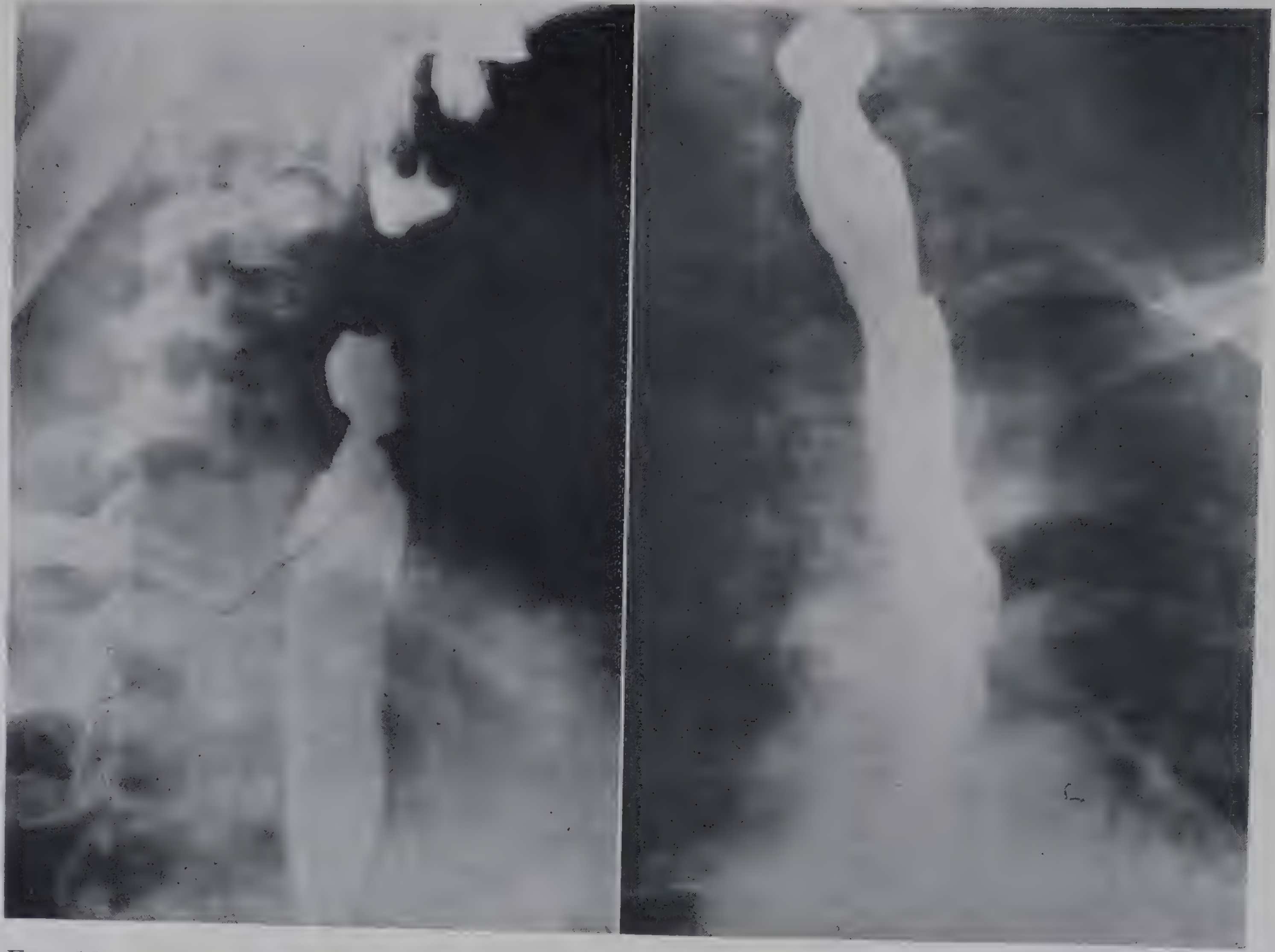

FIG. 19. Same case as Fig. 18; films of esophagus (radiological examination) before and after nearly three months on iron therapy.

tion at this time by Dr. P. Ireland demonstrated a fibrous web at the level of the lower border of the cricoid cartilage, leaving a small opening.

She improved rapidly on administration of ferrous sulphate, 0.3 Gm. t.i.d., and in two months the blood picture became essentially normal. Her spleen slowly became smaller and finally could not be felt; her nails became normal; she became able to tolerate ordinary activity without angina. Another film of the esophagus, taken on June 6 of the same year, when she could swallow much better, shows that the constriction and degree of obstruction had decreased markedly as compared with the February film. She is now (1948) able to eat ordinary meals without dysphagia but occasionally has slight difficulty in swallowing a large chunk of food. Afraid to go without iron, she has taken 0.3 Gm. of ferrous sulphate almost every day for over ten years. She now feels well, with a hemoglobin of 14.5 Gm. per 100 cc.

Most patients tolerate the oral administration of iron well but a few suffer symptoms such as anorexia, malaise, nausea, vomiting, abdominal cramps, constipation, or diarrhea. Such symptoms are often greatly aggravated by fear and apprehension because of the patient's belief that she is unable to take iron. Those that have difficulty can usually be treated successfully with small initial doses of ferrous salts, such as ferrous sulphate or carbonate, 0.065 Gm., given with meals three times a day. The dose is gradually increased, and most patients will soon tolerate effective amounts. It has been claimed[25] that salts such as ferrous gluconate are less apt to give rise to symptoms of intolerance. (The molecule is larger and accordingly greater dosage is required to give the same amount of iron.) Actually ferrous gluconate is effective and may be preferable to the cheaper preparations in rare instances. Very rarely indeed, however, will a physician find difficulty in treating a patient effectively with ferrous sulphate.

When iron is administered parenterally, good effects may be obtained if an adequate dosage be given; 25 mg. of the element iron are required to raise the hemoglobin one point in the average adult, and this amount borders on the toxic dose. Furthermore, injections are painful and the method is not recommended except under exceptional circumstances. An effective dose is 200 mg. of ferrous and ammonium citrate (containing 32 mg. of iron) per day given intramuscularly in two injections. The iron so administered is completely available.

As soon as the patient comes under treatment it is wise to inquire into the dietary history and give clear advice about an adequate diet. As already pointed out, the foods richest in iron are meats, eggs, and leafy vegetables. In any case, the type of diet needed is the general type of diet required for any person of the same age. It is important, however, not to depend on diet alone for relief of the anemia; preparations of inorganic iron must also be administered (see Fig. 20).

CASE REPORT FOR FIG. 20

This 30-year-old male patient had suffered extremely profuse, daily hemorrhoidal bleeding for five years. For three years he had had symptoms of anemia. The hemorrhage ceased after injection of the hemorrhoids on January 24, 1938, but the hemoglobin failed to rise during one month on dietary treatment alone. As shown in the chart (Fig. 20), it responded well to administration of ferrous sulphate which was begun on February 24, 1938.

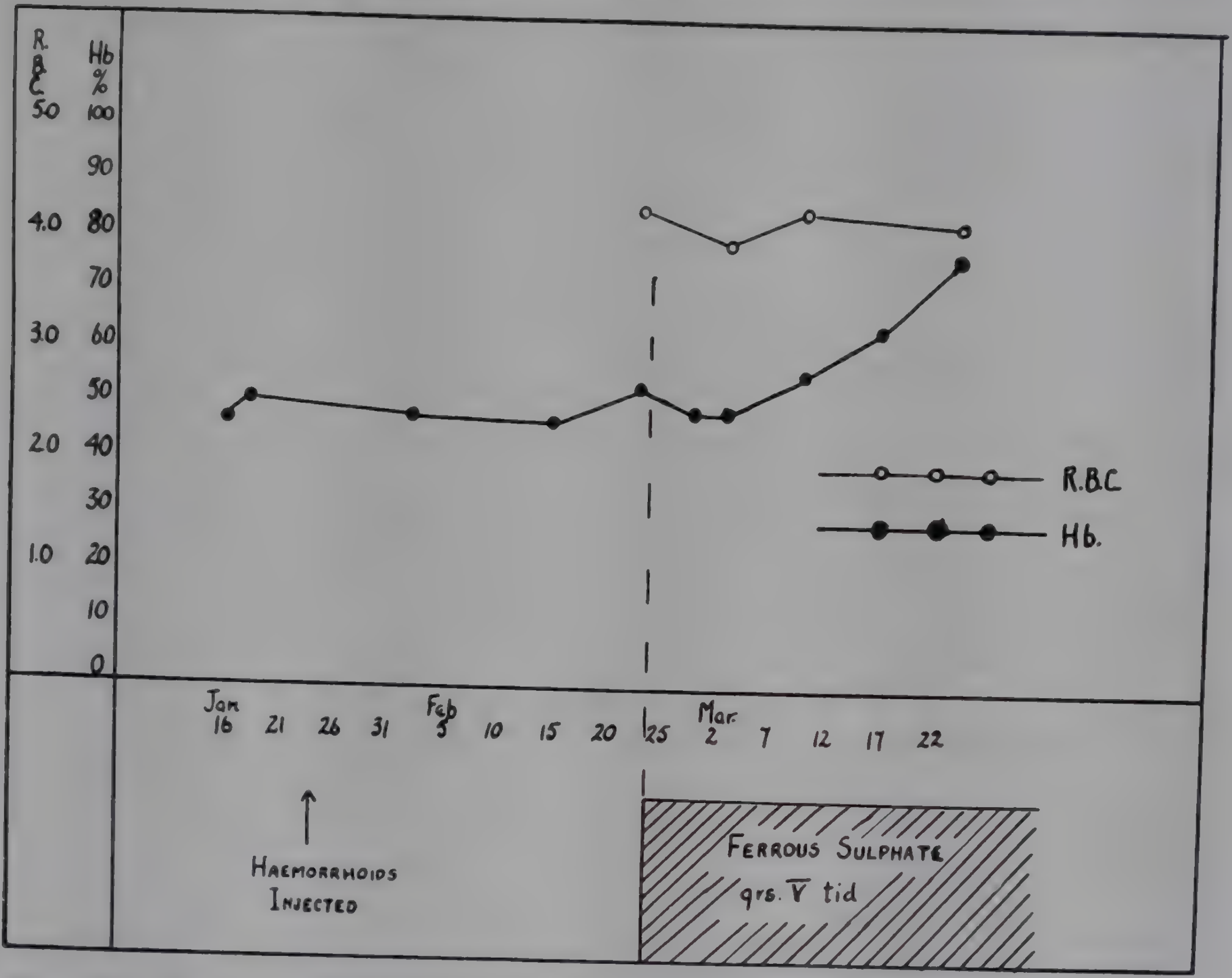

FIG. 20. Posthemorrhagic iron-deficiency anemia. Failure of hemoglobin to rise on cessation of bleeding until after administration of inorganic salts of iron.

Patients with severe anemia should rest most of the time. Activity should be increased, within the patient's tolerance, as the hemoglobin rises and symptoms disappear. Those who have considered themselves invalids for a long time should be encouraged to take gradually increasing exercise till they are able to tolerate a normal activity.

Patients with idiopathic hypochromic anemia of long standing often suffer from the effects of anxiety about their present and future health, commonly worrying particularly about some one organ or system. The doctor should acquire a sympathetic understanding of the patient's point of view and should explain the disorder and all its symptoms to her satisfaction and comprehension. While doing so the physician is often able to give helpful advice about the patient's domestic and social affairs.

It is obvious that, in patients suffering from posthemorrhagic hypochromic anemia, the cause of the severe blood loss must be found and treated. It may be an apparent and relatively unimportant lesion giving rise to severe epistaxis, unusually profuse hemorrhage from hemorrhoids, extreme menorrhagia, etc., or there may be concealed bleeding, possibly from a more serious lesion such as an ulcer or carcinoma in the gastrointestinal tract. It is particularly important that the physician should not consider his responsibility discharged when the hemoglobin has risen to normal unless the site and cause of the bleeding lesion be found and effective treatment given if possible.

It is obviously necessary to give adequate treatment for any associated diseases that may be present.

PREVENTION OF RECURRENCE

Recurrence of a hypochromic anemia is always suggestive of hemorrhage. The institution of a proper general hygienic regimen will often lead to marked improvement in the patient's health and reduction in excessive functional uterine bleeding. More serious causes of menorrhagia or other hemorrhage must be searched for, and treated if found.

Women with idiopathic hypochromic anemia may suffer recurrences from very minor bleeding and during repeated pregnancies. It is desirable to examine the blood at least every three months for a long period after recovery; if the hemoglobin begins to fall, iron should be administered again. Those tending to suffer repeated mild recurrences may often be maintained free from anemia by administration of ferrous sulphate, 0.3 Gm., once a day for the first month in each quarter of the year; during pregnancy they should be given 0.3 Gm. per day till term, and more if required. In cases with any type of uncontrollable hemorrhage, the dosage of iron necessary to prevent hypochromia should be given.

SUMMARY

Iron has been used in treatment of disease since the dawn of history: at first, given empirically; in recent centuries, used as a therapeutic agent in treatment of anemias of all types; only in modern times, as a specific remedy for the distinctive anemia of iron malnutrition which is a hypochromic microcytic anemia.

The metabolism of iron is peculiar in that it is a "one-way substance": it is absorbed from the gastrointestinal tract when needed and never excreted in appreciable amounts. Absorption appears to be controlled by the intestinal mucosa which is able to accept iron in times of need and to reject it when the body's storage regulation is satisfied. Any strain on iron metabolism as a result of prolonged inadequate intake during periods of growth, pregnancy, and lactation, or because of loss of iron in hemorrhage, may lead to iron deficiency with final exhaustion of the available stores and development of a hypochromic anemia.

The chief and often the only clinical manifestations of iron malnutrition are those related to anemia. It must be pointed out, however, that in prolonged severe iron deficiency certain other pathologic changes may occur, such as dystrophy of the nails, and atrophy of the mucous membrane of the tongue and pharynx with development of esophageal webs and dysphagia. Such late changes, whether due directly to iron deficiency or to some secondary effect, are quite specific and, like the anemia, disappear under iron therapy.

Iron malnutrition may occur in both sexes and at any age. In infancy it appears when the fetal storage has been inadequate either because of maternal iron deficiency or premature birth. During childhood and adolescent growth it will occur if the diet contains inadequate amounts of iron or as a result of hemorrhage. In women, from puberty to the menopause, it occurs as a common, probably constitutional, disorder which has been called idiopathic hypochromic anemia. These women usually have achlorhydria, and there appears to be some defect in their regulation of absorption and storage of iron, as a result of which they are more susceptible to minor losses, as in menstruation, pregnancy, and lactation. In other women and in men, iron malnutrition occurs only when the normal iron stores have been exhausted by hemorrhage of greater magnitude.

The hypochromic anemia of iron deficiency can be relieved specifically and promptly by oral administration of preparations of inorganic iron. Transfusions are contraindicated except as emergency measures.

It is important that the physician should not consider that his responsibility is discharged when the hemoglobin has risen to normal. He is responsible always for the general welfare of the patient and for institution of a proper regimen, especially with regard to regulation of diet, rest, and activity, and for alleviation, if possible, of any unfavorable personal, domestic, or social situations. He must search for a bleeding lesion in all cases and especially in all men and older women and, having found its site, give effective therapy if possible.

BIBLIOGRAPHY

1. ALLBUTT, T. C. System of Medicine. New York, Macmillan, 1905, p. 479.
2. ASHWELL Observations on chlorosis and its complications. *Guy's Hosp. Rep.* 1:529, 1836.
3. BALFOUR, W. M., HAHN, P. F., BALE, W. F., POMMERENKE, W. T., and WHIPPLE, G. H. Radioactive iron absorption in clinical conditions: normal, pregnancy, anemia and hemochromatosis. *J. Exper. Med.* 76:15, 1942.
4. BLACKFAN, K. D., DIAMOND, L. K., and LEISTER, C. M. Atlas of the Blood in Children. New York, Commonwealth Fund, 1944.
5. CHRISTIAN, H. A. A sketch of the history of the treatment of chlorosis with iron. *Med. Libr. and Hist. J.* 1:176, 1903.
6. DAMESHEK, W. Primary hypochromic anemia (erythro-normoblastic anemia). *Am. J. M. Sc.* 182:520, 1931.
7. DARBY, W. J. The oral manifestations of iron deficiency. *J.A.M.A.* 130:830, 1946.
8. DAUPHINEE, J. A. The iron requirement of normal nutrition. *Canad. M. A. J.* 39:483, 1938.
9. DAVIES, D. T. Studies on achlorhydria and anaemia. *Quart. J. Med.* 24:447, 1931.
10. DAVIES, D. T. Simple achlorhydric anaemia. *Lancet* 2:389, 1931.
11. DUBACH, R., MOORE, C. V., and MINNICH, V. Studies in iron transportation and metabolism: V. Utilization of intravenously injected radioactive iron for hemoglobin synthesis, and an evaluation of the radioactive iron method for studying iron absorption. *J. Lab. & Clin. Med* 31:1201, 1946.
12. GRANICK, S. Ferritin: its properties and significance for iron metabolism. *Chem. Rev.* 38:379, 1946.
13. GRANICK, S. Ferritin: increase of the protein apoferritin in the gastrointestinal mucosa as a direct response to iron feeding. The function of ferritin in the regulation of iron absorption. *J. Biol. Chem.* 164:737, 1946.
14. HAHN, P. F. The metabolism of iron. *Medicine* 16:249, 1937.
15. HAHN, P. F., BALE, W. F., LAWRENCE, E. O., and WHIPPLE, G. H. Radioactive iron and its metabolism in anemia. *J. Exper. Med.* 69:739, 1939.
16. HAHN, P. F., BALE, W. F., ROSS, J. F., BALFOUR, W. M., and WHIPPLE, G. W. Radioactive iron absorption by gastrointestinal tract. *J. Exper. Med.* 78:169, 1943.
17. HAHN, P. F., and WHIPPLE, G. H. Iron metabolism. *Am. J. M. Sc.* 191:24, 1936.
18. HEATH, C. W., and PATEK, A. J. The anemia of iron deficiency. *Medicine* 16:267, 1937.

19. MACALLUM, A. B. On the absorption of iron in the animal body. *J. Physiol.* 16:268, 1894.
20. MCCANCE, R. A., and WIDDOWSON, E. M. Absorption and excretion of iron. *Lancet* 2:680, 1937.
21. MEULENGRACHT, E. Large doses of iron in different kinds of anaemia in a medical department. *Acta med. Scandinav.* 58:594, 1923.
22. MINOT, G. R., and HEATH, C. W. The response of the reticulocytes to iron. *Am. J. M. Sc.* 183:110, 1932.
23. MOORE, C. V., DUBACH, R., MINNICH, V., and ROBERTS, H. K. Absorption of ferrous and ferric radioactive iron by human subjects and by dogs. *J. Clin. Investigation* 23:755, 1944.
24. N.R.C. Committee on Food and Nutrition. Recommended daily allowances for specific nutrients. *J.A.M.A.* 116:2601, 1941.
25. OSLER, W. "Diseases of the blood and blood glandular system," in *Pepper's System of Practical Medicine*, 1885, p. 882.
26. REZNIKOFF, P., and GOEBEL, W. F. The use of ferrous gluconate in the treatment of hypochromic anemia. *J. Clin. Investigation* 16:547, 1937.
27. SHOHL, A. T. Mineral Metabolism. New York, Reinhold, 1939.
28. STOCKMAN, R. Treatment of chlorosis. *Brit. M. J.* 1:881 and 942, 1893.
29. STOCKMAN, R. The causes and treatment of chlorosis. *Brit. M. J.* 2:1473, 1895.
30. STOCKMAN, R. Summary of sixty-three cases of chlorosis. *Edinburgh M. J.* 1:1077, 1895.
31. STOCKMAN, R. The iron in the liver and spleen. *Brit. M. J.* 1:1077, 1896.
32. SUZMAN, M. M. Syndrome of anemia, dysphagia and glossitis. *Arch. Int. Med.* 51:1, 1933.
33. WHIPPLE, G. H., and ROBSCHUT-ROBBINS, F. S. Blood regulation in severe anemia: VIII. Influence of bone-marrow, spleen, brains and pancreas. The question of inorganic iron in the diet. *Am. J. Physiol* 80:391, 1927.
34. WHIPPLE, G. H., and ROBSCHUT-ROBBINS, F. S. Iron and its utilization in experimental anemia. *Am. J. M. Sc.* 191:11, 1936.
35. WINTROBE, M. M., and BEEBE, R. T. Idiopathic hypochromic anemia. *Medicine* 12:187, 1933.
36. WITTS, L. J. The constitutional factor in diseases of the blood. *Practitioner* 129:450, 1932.
37. WITTS, L. J. Therapeutic action of iron. *Lancet* 1:1, 1936.

Chapter 12

SODIUM, POTASSIUM, AND CHLORIDE MALNUTRITION, INCLUDING WATER BALANCE AND SHOCK

James Arnold Dauphinee

When the various states of malnutrition are considered, it is not usual to think of those which are caused by lack of such common things as water and ordinary salt. The reason, of course, is that among otherwise healthy persons, except under exceptional circumstances, disturbances due to inadequate intake of these substances are not frequently encountered. However, in a wide variety of illnesses an intake of water and of salt that is insufficient to meet the normal or increased metabolic needs or, more commonly, inadequate to make up for excessive losses, leads to the occurrence of clinical signs and symptoms which can quite properly be considered as being evidence of a specific malnutrition. When it is remembered that inadequate nutrition with salt and water may be associated with such important clinical disturbances as dehydration, edema, alkalosis, acidosis, shock, oliguria and anuria, uremia, fever, and with many others, no excuse need be offered for the inclusion in this book of a chapter on the physiology, etiology, clinical picture, and treatment of conditions caused by lack of these substances.

HISTORICAL

The empirical recognition of the importance of water and of salt in human nutrition goes back to ancient times. The need for the ingestion of adequate amounts of water and the disastrous results which followed any prolonged deprivation of fluid were obvious to everyone. The need for salt was not quite so apparent, but an appetite for this mineral, as real as for any other food, was possessed by all peoples. However, it was more marked in some than in others and the nomadic races who consumed raw or roasted meat and drank milk, both of which contain moderate amounts of sodium salts, did not often require more salt than that contained in their food. Agricultural people, on the other hand, who subsisted largely on sodium-poor cereals and vegetables, actually needed, particularly when they lived in hot climates, the extra salt which they so eagerly sought as a condiment and for which many sacrifices would be made. This difference is obvious today among animals. The carnivora pay little attention to salt whereas the herbivorous animals will travel long distances in order to satisfy their salt hunger.

By the term "salt" of course is meant sodium chloride. Although it is now known that potassium salts are also very important in nutrition, no separate need for them was recognized by early peoples simply because all natural foodstuffs contain potassium in considerable amounts and any diet which provided enough food to maintain life also provided ample amounts of this element.

The importance of sodium chloride among the ancient peoples was indicated in many ways. Cakes of salt are said to have been used for money. Men at times traded their wives and children into slavery for salt. Taxes were levied on it and it was included among the offerings to the gods. In the second chapter of Leviticus the directions given to Moses concerning the offerings to the Lord included: "And every oblation of thy meat offering shalt thou season with salt; neither shalt thou suffer the salt of the covenant of thy God to be lacking from thy meat offering: with all thine offerings thou shalt offer salt" (Lev. 2:13). It is, however, only in recent times that careful studies by such investigators as Gamble and his co-workers,[19-21] Peters,[38, 39] Darrow,[10-12] McCance,[28, 29, 32] Marriott,[33] Butler and Talbot,[6, 7] and many others, have led to a precise understanding of the roles played by sodium chloride and other salts in the living organism and have made us aware of the manner in which deficiencies of these substances may contribute to human illness.

GENERAL CONSIDERATIONS

The bodies of all living things contain large amounts of water and varying amounts of inorganic materials including the chlorides and other salts of sodium and potassium. Although these substances are essential constituents of all tissues, water and salts are not ordinarily thought of as foodstuffs in the strict sense of the term. They do not undergo combustion to supply energy as do the carbohydrates, fats, and proteins. They undergo no essential change in the body and they are excreted in the same form as that in which they are ingested, but when it is remembered that in passing from infancy to maturity the growing human incorporates into his body about 40 to 50 Kg. of water, about 60 to 70 Gm. of sodium, 70 to 80 Gm. of chlorine, and 140 to 150 Gm. of potassium,[42] it is obvious that these substances may properly be considered as being foodstuffs which, although they are utilized in relatively small amounts, are just as necessary as are the other tissue-building and energy-producing foods.

Water and salt are then essential materials from a purely structural point of view, but they are obviously much more important than mere building materials. All the complicated biochemical and biophysical reactions which are constantly going on in a living individual, which when functioning harmoniously together constitute life, proceed normally only when the temperature, water and electrolyte concentration, osmotic pressure, hydrogen-ion concentration, and other properties of the interstitial fluids which bathe every living cell are kept within very narrow limits. This conception of the necessity of a fixed or constant internal environment for normal health and life, first enunciated by Claude Bernard, is one of the most important principles of physiology. The maintenance of the constancy of this internal environment requires the ceaseless functioning of elaborate regulating mechanisms which not only depend upon the presence in the body of adequate amounts of water and of various electrolytes, but also involve the constant excretion of considerable quantities of these substances in the urine, expired air, sweat, and feces. If insufficient amounts of these substances are ingested to maintain the necessary levels in the body, or excessive amounts are lost or excreted, the internal environment of the cells will change and the signs and symptoms of the condition known as "dehydration" will be produced. Such a dehydration may constitute the primary clinical problem, but much more frequently it is secondary to other disease and adds considerably to the difficulties of the already sick patient. The successful treatment will depend to a large degree upon the ability of the physician to recognize and correct these disturbances, and this must often be done before more specific and curative measures can be undertaken. Such correction can be accomplished successfully only if the underlying mechanisms of production and the disturbed chemistry associated with these phenomena be properly understood, and for this reason considerable space is devoted in this chapter to a consideration of water balance and of the relationships which exist between water and salt metabolism.

PHYSIOLOGY

BODY COMPARTMENTS

The water of the body, which makes up about 70 per cent of the total weight of the adult, is distributed between two main systems or compartments. By far the greatest portion is found within the tissue cells and is spoken of as the *intracellular fluid*, whereas the water which is outside the cells is said to be in the *extracellular* compartment. The extracellular fluid also exists in two separate portions—the *intravascular* portion in the blood plasma, and an *interstitial* portion outside the blood vessels within the tissue spaces. The amount of water normally present in these compartments is given in Table 20.

TABLE 20. APPROXIMATE AMOUNT OF WATER IN DIFFERENT BODY COMPARTMENTS

70 KG. ADULT

Compartment	*Volume of fluid* (cc.)	*Percentage of body weight*
Intracellular	35000	50
Extracellular		
Plasma	3500	5
Interstitial	10500	15
Total body water	49000	70

COMPOSITION OF FLUID IN THE COMPARTMENTS: NORMAL VALUES

The concentration of the inorganic salts (which are almost completely dissociated into acidic and basic ions) in this body water can be expressed as so many mg. per 100 cc., commonly abbreviated to "per cent" (or so many vols. per cent in the case of bicarbonate) but the relationship between the various ions can be more easily understood if the amounts present are given in terms of milliequivalents per liter (mEq/L) of fluid.* As 1 mEq of any basic ion is equivalent to 1 mEq of any acid ion and as the blood is nearly neutral in reaction, the sum of all the basic ions in the blood serum is approximately equal to the sum of all the acid ions.

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* This value is readily obtained by the following calculation: $mEq/L = \frac{mg.\ \% \times 10}{atomic\ wt.} \times valency$; e.g. if the sodium content of a given sample of serum is found to be 320 mg. per cent the concentration in terms of mEq/L would be $\frac{320 \times 10}{23} \times 1 = 139.1$; or if the calcium content is 10 mg. per cent the concentration would be $\frac{10 \times 10}{40} \times 2 = 5$ mEq/L.

The principal inorganic constituents of the extracellular fluids including the lymphatic fluid and spinal fluid as well as the secretions of the various digestive and other glands, are sodium and chlorine ions (the normal concentrations of which are given in Table 21) whereas in the intracellular water, potassium, magnesium, phosphate, and sulphate ions predominate. It is important to remember that the inorganic content of these various fluids is such that they are all isotonic with one another and that therefore the loss of 1000 cc. of intestinal fluid by diarrhea causes the loss of an amount of sodium salts similar to that contained in an equal volume of blood.

TABLE 21. APPROXIMATE SODIUM, POTASSIUM AND CHLORIDE CONTENT OF EXTRACELLULAR FLUIDS

(FROM THE LITERATURE)

	Sodium		*Potassium*		*Chlorine* as Cl	
Fluid	mEq./L.	mg. %	mEq./L.	mg. %	mEq./L.	mg. %
Blood serum	138–142	310–330	3.5–5.5	13.5–21.5	95–105	340–370
Spinal fluid	147	338	2.8	11	125	443
Gastric juice	20	46	8	31	145	514
Hepatic bile	140	322	8	31	108	383
Pancreatic juice	140	322	5	19	40	142
Jejunal juice	138	317	5	19	110	390
Sweat	70	161	5	19	65	230
Saliva	105	240	—	—	80	284

Normally the marked difference in the inorganic composition of the fluids in the extracellular and intracellular compartments is well maintained because they are separated from one another by semipermeable membranes which, although permitting the passage of water, glucose, and other metabolites do not readily allow the passage of sodium and potassium ions. Under certain circumstances, however, which will be discussed later, both these ions may pass this boundary in relatively large amounts.

WATER BALANCE

SOURCES OF WATER

Some of the water available to the body comes from the so-called solid foods, many of which, like the living individual, are made up largely of water. The green vegetables contain 90–98 per cent water and even meat is approximately 50 to 70 per cent water. A smaller amount is derived from the oxidation of the hydrogen in carbohydrates, fats, and proteins, which yield respectively 55, 107, and 41 Gm. of water for every 100 Gm. that are burned. The balance of the necessary daily intake, usually the largest portion, is taken in the form of various fluids.

WATER LOSSES

In health, water is constantly being lost from the body by the several normal excretory channels. In disease, the amounts lost in these ways may be markedly increased and there may also occur losses by abnormal channels.

1. *Evaporation from the skin and in the respired air:* As an important part of the temperature-regulating mechanism a certain loss of water by evaporation from the skin is inevitable. (See Chapter 28 for a more detailed discussion of insensible perspiration.) The amount will vary greatly with the circumstances, but it is never inconsiderable and it may be very high. It will depend upon the heat produced in the body, that is, upon the height of the body metabolism, and also upon the efficiency of the other mechanisms for losing heat (which will depend upon air temperature and humidity). Adults with normal metabolism lose even in cool climates 500 to 600 cc. water daily in this way by the evaporation of the so-called insensible perspiration. When the individual lives or works in a place where the air temperature is high or when his metabolism is increased by hard work, fever, or other illness, the loss in the form of visible sweat may be very much greater.

Not only is water being constantly lost by evaporation from the skin, but it is also excreted in the expired air. It is obvious that this loss, which amounts to 400 to 500 cc. daily under ordinary circumstances, will go on as long as the individual continues to breathe and also that the extent of this loss may be increased by any condition, such as fever or increased metabolism, which increases the temperature or volume of the respired air.

2. *Excretion in the urine:* The volume of water which must be sacrificed daily for the formation of urine will depend not only upon the amount of waste products which must be excreted but also upon the degree to which they can be concentrated by the kidney. The normal kidney is able, when only limited quantities of water can be spared from the body, to conserve water by producing a urine of which the specific gravity may be as high as 1036 or 1038[32, 36] but these are maximal figures and cannot be exceeded nor kept up indefinitely. If retention of waste products in the body is to be avoided the minimal amount of water

which must be excreted daily by a person with normal kidneys is approximately 600 to 700 cc. If water in excess of these amounts is available, it too will be excreted and the urine will then have a higher volume but a lower specific gravity and a lower concentration of total solids. If less water than the minimal amount necessary can be spared, the urine volume will drop and there will be an increase in the levels of the blood nonprotein nitrogen. Even in the complete absence of all water intake, normal kidneys continue to excrete about 300 to 500 c.c. urine daily as long as the blood pressure remains high enough to produce a glomerular filtrate.

Whereas the normal person can when necessary reduce his daily urinary output to 600 to 700 cc. and still excrete in it the necessary amounts of solids because he is able to concentrate them into a relatively small volume of water, those individuals who have certain forms of renal disease such as chronic nephritis, and who are therefore unable to concentrate these solids to the same degree, must excrete a considerably higher volume of urinary water if they are to avoid nitrogen retention. The lower the ability of the kidney to concentrate the urine the higher must the ratio be between the water and solids excreted. The data of Lashmet and Newburgh[27] illustrate this very well. They have shown that although only 625 cc. water are required to excrete 50 Gm. solids in a urine of which the specific gravity is 1032, over 2000 cc. are required for the excretion of the same weight of solids if the specific gravity cannot be raised above 1010. A similar loss of renal concentrating power, associated with an obligatory increase in the excretion of urinary water, may also be encountered in patients who have partially recovered from prolonged surgical shock or from a period of severe dehydration.

Serious losses of water may also occur through excessive renal excretion in patients suffering from untreated diabetes mellitus or diabetes insipidus. In uncontrolled diabetes mellitus the high blood sugar levels lead to the excretion of such large amounts of sugar into the glomerular filtrate that it cannot all be reabsorbed by the tubules. The presence of this excessive amount of sugar in the tubules prevents, by reason of the osmotic pressure which it exerts, the normal reabsorption of water, with the result that excessive quantities of water, which may amount to many liters, are excreted in the urine. In diabetes insipidus the reabsorption of water is also interfered with because of damage to the posterior lobe of the pituitary gland or related structures, and large volumes of very dilute urine of low specific gravity and containing very little chloride are excreted. The daily output is usually between 5 and 10 L. or more and the fluid intake has to be increased accordingly to prevent a negative water balance and rapid water depletion.

3. *Excretion with the feces:* Under ordinary circumstances the loss of fluid in the feces is small—usually less than 100 cc. daily. If a state of diarrhea should occur, however, it is obvious that the water loss in this way may be much greater than normal and may reach proportions which if not counteracted by an increased intake will deplete the body water very rapidly.

4. *Abnormal losses of water:* Some of the ways by which abnormal losses of water may occur, such as increased sweating, increased loss in the urine, and increased excretions in the feces, have already been mentioned. Additional losses may of course occur as the result of vomiting, from draining fistulas, and from repeated tappings of collections of fluid in the abdominal or thoracic cavities. Considerable water as well as protein and electrolyte is lost in the exudate of extensive surface burns. Water is also lost whenever there is hemorrhage, and a concealed loss which may be of real importance is brought about by the exudation of fluid into tissues which have been the site of traumatic or other injury.

THE MINIMAL REQUIREMENT OF WATER

There is thus seen to be a continuous and unavoidable loss of water from the skin, in the respired air, and in the urine, which cannot be prevented or stopped, or decreased beyond a certain irreducible minimum if normal function is to be preserved. The magnitude of the total loss varies considerably, but it will certainly be not less than 1500 to 2000 cc. for an adult at bed rest on a low calorie diet, and it will be increased by anything, such as exercise, hyperthyroidism, or fever, which raises the metabolism. It will be also increased whenever there is excessive sweating, low renal efficiency, or increased loss through abnormal channels.

In infants and children the minimal water losses per unit of weight are considerably greater than they are in adults because of the higher metabolic rate, the proportionately larger surface area from which water may evaporate, the extra demands for growth, and, in very young babies, because of the lessened power of the kidney to produce a concentrated urine.[31] However, if the necessary water expenditure is related to the total metabolism rather than to weight, the minimal water loss is, as has recently been emphasized by Darrow,[12] the same in both babies and adults and amounts to about 80 to 170 cc., depending upon the urine specific gravity, per 100 calories of energy output.

These losses must be balanced by an intake of water from all sources which must be at least equal to the amount lost, for the body cannot tolerate any marked decrease in its water content. A loss of 10 per cent of the body water will produce serious symptoms, and a loss of 20 per cent will often prove fatal. It is of course desirable that the intake be considerably higher than this minimal requirement so as to provide a moderate excess. As long as no condition is present which interferes with the normal excretion of water, any excess of intake over the requirement is rapidly eliminated by the kidneys.

TABLE 22. APPROXIMATE NORMAL LOSSES AND ALLOWANCES PER DAY* FOR PERSONS OF VARYING SIZE NOT SUBJECT TO EXERTION OR SWEATING

	Water loss cc.				*Usual water allowance*		
Size	Urine	Stool	Insensible	Total	cc./person	cc./Kg.	oz./lb.
Infant 2-10 Kg.	200-500	25-40	75-300†	300-840	330-1000	165-100	2.5-1.5
Child 10-40 Kg.	500-800	40-100	300-600	840-1500	1000-1800	100-45	1.5-0.7
Adolescent or adult 60Kg.	800-1000	100	600-1000‡	1500-2100	1800-2500	45-30	0.7-0.5

From Butler and Talbot.[6]

* Including water content and water of oxidation of food which under normal circumstances except for infants approximates the insensible water loss.

† 1.3 cc. per Kg. per hr.

‡ 0.5 cc. per Kg. per hr.

TABLE 23. WATER BALANCE
70 KG. ADULT

Intake cc.		*Excretion* cc.		*Possible abnormal losses* cc.
As fluids	1500	Urine	1500	(Diuresis 3000–15,000)
In solid foods	800	Vaporization		
From combustion	300	Skin	600	(Excessive sweating 5000–10,000)
		Lungs	400	
		Feces	100	(Diarrhea 5000)
				(Vomiting 5000)
				(High Fistula 5000)
Total	2600		2600	

The approximate normal water losses and minimal allowances per day for persons of varying size are given in Table 22, and in Table 23 are given figures which indicate approximately the source and amount of water which may be taken in by a normal adult at rest in a temperate climate, and the amounts which may be excreted by the various routes under the same circumstances. The figures in the third column of Table 23 indicate the magnitude of some of the abnormal losses which may be experienced.

Sodium, Chlorine, and Potassium Balance

SOURCES OF SODIUM, CHLORINE, AND POTASSIUM

These elements are present in varying amounts in almost all the constituents of a normal diet. The values given by different authorities for the amount of these minerals to be found in the various foods, although all of the same general magnitude, show considerable variations which are particularly large in the case of sodium. In spite of these variations,

TABLE 24. SODIUM AND POTASSIUM IN COMMON FOODS*

Food	*Mineral content* Na. mg%	K. mg%
Nuts		
Almonds	2.0	690
Brazil nuts	0.8	650
Filberts	0.8	560
Peanuts (unsalted)	0.8	740
Walnuts	2.0	450
Fruits		
Apples	0.1	68
Apricots	0.5	440
Bananas	0.1	400
Cherries	1.0	280
Lemons	0.6	130
Oranges	0.2	170
Peaches	0.1	180
Plums	0.1	140
Strawberries	0.7	180
Cereals		
Barley	3.0	160
Corn	0.4	290
Oats	2.0	340
Rice	0.8	100
Wheat	2.0	430
Legumes		
Beans, in pod	0.8	300
Lima beans, fresh	1.0	700
Navy beans, dry	0.9	1300
Peas, fresh	0.9	380
Green leafy vegetables (edible portion)		
Broccoli	16	400
Cabbage	5	230
Cauliflower	24	400
Lettuce	12	140
Spinach	190	790
Celery stalks	110	300
Root vegetables (less skins)		
Beets	110	350
Carrots	31	410
Potatoes	0.6	410
Turnips (yellow)	5	260
Hen eggs		
Whole egg (less shell)	140	130
Milk and milk products		
Human milk	40	64
Cow's milk	51	140
Butter (unsalted)	5	4
Butter (salted)	980	—
Cheese (cheddar)	540	130
Cheese (cottage)	320	80
Meats and fish (less bone and excess fat)		
Beef	53	380
Chicken leg	110	250
Cod	60	360
Calf liver	110	380
Lamb	110	340
Pork	58	260
Turkey leg	92	310

* Values taken from tables published by the Research Laboratory, Mead Johnson and Co., May, 1947.

which are probably due at least in so far as the vegetables are concerned to the nature and salt content of the soil in which they have been grown, there is general agreement that the amount of sodium and of chlorine in most of the foods of plant origin, especially nuts, fruits, cereals, and legumes, is very low whereas foods from animal sources are relatively rich in these minerals. In foods which contain much potassium and very little sodium, perhaps especially fruits and vegetables, the true amounts of sodium in the natural raw food are apt to be even less than the figures found in reference tables, because the analytic methods hitherto preferred tend to overestimate sodium in such cases. The results of a recent series of determinations of sodium and potassium, obtained by the use of the flame photometer at the Mead Johnson and Company Research Laboratory in a variety of foods, are given in Table 24.

In addition to these natural sources of sodium and chlorine, supplementary amounts of these elements are usually taken in as a result of the liberal use of salt in cooking and at the table. Foods which are cooked or eaten without this condiment seem flat and tasteless to most people. For this reason most foods before being eaten are liberally flavored with salt.

The average adult intake of sodium chloride from all sources, including that present naturally in the food and that which is used in normal cooking and at the table, amounts to about 8–15 Gm. per day.

Table 24 also shows that the potassium content of almost all foods is considerable and, in the vegetable foods particularly, it is much higher than that of the sodium. The intake of potassium by the average adult on an ordinary diet is about 2–4 Gm. daily and any diet which would contain much less than this would have to be prepared from specially selected or purified foods.

SODIUM, CHLORINE, AND POTASSIUM EXCRETION

1. *In the urine:* (a) *Sodium and chlorine:* Sodium chloride is normally eliminated almost entirely by the kidneys, although small amounts are found also in the feces and in the sweat. The amount of salt which is excreted by the kidneys in health, in the absence of any significant sweating, is determined entirely by the level of the salt intake. When the intake is constant the amount of salt excreted in the urine is, within narrow limits, equal to the intake. If the intake is increased or decreased a balance is soon established at a new level after a few days, when once more the intake and excretion are approximately the same. Although such changes in the salt intake may be associated with a retention or loss of a small amount of the total body salt (which will be accompanied by a corresponding change in the amount of body water), the renal mecha-

nism for regulating the level of salt in the body is so effective that a salt balance is maintained over a wide range of intake. When the intake is stopped entirely, as it is in starvation, the plasma concentration drops somewhat from the normal level of 580–600 mg. per cent (the concentration, expressed as NaCl, usually found when the intake of salt is normal) down to the lower limit of normal of about 560 mg. per cent or somewhat lower. As the level of the blood sodium chloride falls, the excretion of salt in the urine gradually decreases until, at a point where the blood levels have reached low normal values, it almost stops. This is well shown by the observations made by Benedict[2] on the chloride excretion in the urine of his subject L. during a thirty-day fast when distilled water was the only substance ingested. The salt excretion of L. dropped from over 6 Gm. on the first day to about 0.5 Gm. on the tenth day. During the next ten days the average excretion of NaCl was 0.35 Gm. daily and during the final ten days the excretion was only 0.25 Gm. per day.

The almost complete disappearance of sodium and chlorine from the urine of normal persons whose intake of salt is very low is due to the very efficient regulatory mechanisms which control the reabsorption by the renal tubes of these ions from the glomerular filtrate. These mechanisms so function that when the plasma concentrations of these substances have fallen to low normal values, the reabsorption is almost complete and only traces of these elements find their way into the urine. If the plasma levels tend to rise as the result of an increased intake the tubular reabsorption becomes less complete and more salt is permitted to escape with the excreted water. In this way the kidneys control the excretion of sodium and of chlorine so that their concentration in the blood and other extracellular fluids is kept within relatively narrow limits. It is for this reason that serious sodium chloride depletion is never encountered in normal humans as a result of a low intake unless salt is being lost through some other channels.

This activity of the kidney, which prevents further loss of sodium chloride in the urine when there is a threatened depletion, is controlled in part at least by the hormones of the adrenal cortex. Animals suffering from adrenal insufficiency produced by adrenalectomy show an increased urinary excretion of sodium chloride which continues even after the blood levels have fallen below normal, and they pass rapidly into a state of sodium depletion from this cause unless the abnormal losses so produced are compensated for by an increased intake of salt. Humans suffering from Addison's disease caused by atrophy or tuberculosis of the adrenal cortex also exhibit these exaggerated losses of salt in the urine and the clinical manifestations of their disease are due in large measure to the salt depletion so produced.

Because all nonvolatile acids have to be excreted by the kidney in the form of salts, the sodium losses in the urine may be increased in conditions of acidosis, particularly if, as is not uncommon in advanced chronic nephritis, the ammonia-forming ability of the kidney is impaired.

(b) *Potassium:* Ingested potassium salts are also rapidly excreted by the urine, and a balance between intake and output is maintained in much the same way as with sodium salts except that the blood levels of potassium are kept normally at the much lower values of 14–20 mg. per cent or 3.5–5 *mEq/L*. However, during fasting the excretion of potassium, although decreased, does not like that of sodium virtually cease but continues instead at a rate which, by reason of its quantitative relation to the amount of nitrogen excreted at the same time, indicates that it must come from the destruction of cellular protein. This is evidence of the continuous endogenous metabolism which goes on during fasting and indicates a gradual breakdown of tissue cells. Any other condition which is associated with damage or death of tissues or with cellular dehydration also permits an escape of cellular potassium into the extracellular fluids, and because the renal threshold for this ion is low it is excreted by the kidneys and is thus lost to the body. In this way serious losses of potassium can occur which if sufficiently great may lead to the appearance of the clinical manifestations of potassium deficiency. These will be discussed in a later section.

2. *In the feces*: Of the total output of these substances only 1–2 per cent of the sodium and chlorine and 6–10 per cent of the potassium is found in the stools under normal conditions. When diarrhea occurs, however, the excretion of all three substances in the liquid stools is markedly increased, and the excessive losses produced in this way may be responsible for the appearance of clinical syndromes caused by deficiencies of these elements.

3. *In the sweat:* Very little salt is lost in the so-called insensible perspiration, but the water of visible sweat contains sodium chloride in amounts which vary from about 0.1 to 0.4 per cent, along with a small amount of potassium chloride. The losses of salt through the skin are normally very small but if there is excessive sweating, no matter how produced, the excretion of sodium chloride in this way may reach as high as 10–30 Gm. per day.

The Minimal Requirement of Sodium, Chlorine, and Potassium

It is difficult to give any figures which indicate accurately the minimal human requirement of sodium, chlorine, and potassium. Although they are extremely important in nutrition the actual amount of these substances in the body is very small and because they are found in almost all foods spontaneous deficiencies are never observed in otherwise normal people.

As might be expected, animal experiments have shown by the use of specially purified diets that all three of these substances are necessary for life, but the amount required to permit normal growth and maintenance is very small. The human infant must add to his tissues considerably less than one tenth gram of each daily to meet the needs of growth, and it would appear that the normal healthy adult can be maintained in mineral balance as far as these elements are concerned on intakes which are no larger than 1 Gm. per day, an amount which is only a fraction of that contained in even the poorest of diets. The allowances recommended for normal maintenance, however, are, in the absence of cardiac and renal disease, higher than these minimal requirements so as to permit a considerable margin of safety. Butler and Talbot[6] suggest a maintenance intake for an infant of 1 Gm. and for an adult 6 Gm. sodium chloride daily. When for any reason there are abnormal or excessive losses the intake necessary to meet the requirement may of course be very much increased.

Sodium and Chlorine and Their Relation to Body Water and Acid-Base Balance

The main functions of sodium and chlorine in the body are related to the regulation of body water and the control of the plasma volume, the regulation of the osmotic pressures of the extracellular fluids, and the mechanisms associated with the buffer reactions of the body. Apart from these, and the long-known association between sodium chloride and cardiac contractility, it is very difficult to assign to sodium or to chlorine any other specific role in human nutrition.

SODIUM CHLORIDE AND BODY WATER

1. *Sodium chloride and extracellular fluid volume:* The principal inorganic constituents in the extracellular water are sodium salts, and these are responsible for most of the electrolytic osmotic pressure exerted by the fluid in this compartment. As has been indicated earlier, a fundamental requirement for cellular health is the maintenance of this osmotic pressure within relatively narrow limits. This means that if the amount of sodium salts (the most important of which is sodium chloride) in the body is permitted for any reason to increase there must occur at the same time an increase in the volume of the extracellular water in order that the normal osmotic pressure be preserved. Similarly, if the sodium chloride content of the body is diminished there must be a decrease in the

amount of the extracellular fluid. One of the main results, then, of sodium depletion is a decrease in the volume of the total extracellular fluid, a decrease which is experienced not only by the interstitial fluid but by the circulating blood plasma as well.

2. *The relation between the extracellular electrolytes, the intracellular fluid, and the distribution of body water:* The amount of sodium salts present in the body not only regulates the volume of the extracellular fluids, but it exerts a considerable influence on the intracellular water as well. Normally these two fluids are in osmotic equilibrium. If the concentration of salt in the extracellular fluids is changed, as it will be as a result of water deprivation or excessive salt loss, then (as sodium does not readily pass through the cell membrane) water will pass from the cells to the interstitial fluid or vice versa until the equilibrium is once more restored. For this reason marked disturbances in the distribution of body water may occur as a result of dehydration, and the nature of this disturbance depends, as was pointed out by Kerpel-Fronius[25] in 1935, to a great extent upon whether the dehydration is associated mainly with water depletion on the one hand or with sodium depletion on the other.

(a) *Water depletion:* If a decrease in the water content only of the blood has occurred (as a result for instance of water deprivation), the blood volume will be restored from the interstitial fluid by the osmotic activity of the plasma proteins. However, such water loss will produce an increase in the salt concentration not only of the blood, but also, because the capillary walls are fully permeable to sodium and chloride ions, of the whole extracellular fluid. As a result, water is drawn from the cells into the now relatively hypertonic interstitial tissues until the water originally lost is largely restored by water which has come from the body cells. The dehydration in this way involves the cells as well as the blood and interstitial tissues, and the volume of the extracellular fluid including the blood plasma is relatively well maintained at the expense of the cellular water. In such conditions a significant decrease in blood volume occurs only as a late manifestation of severe general body dehydration.

(b) *Salt depletion:* If, on the other hand, salt-containing fluids are lost from the body and either are not replaced at all or are replaced by water only, the salt concentration of the extracellular fluids will be unchanged or even decreased. There will be therefore not only no shift of water from the cells to the extracellular compartment to compensate for the loss of fluid, but the volume of the extracellular fluid may be even further diminished by a shift of water from the interstitial spaces to the now relatively hypertonic cells. Thus the bulk of the fluid lost—and even more—is drawn from the extracellular compartment, and a loss which may be small in relation to the total body water will lead to a comparatively marked decrease in the volume of the fluid in the whole of the extracellular compartment.

Because of the presence of the plasma proteins, the osmotic pressure of which tends to keep the water within the blood vessels, the decrease in the volume of the blood plasma is not as marked as it is in the interstitial portion of the extracellular fluid. It may be considerable, nevertheless, and the main clinical manifestations of salt loss are due to this decrease in the volume of the blood plasma and the circulatory disturbances which are caused by this change.

SODIUM CHLORIDE AND ACID-BASE BALANCE

The maintenance of the proper hydrogen-ion concentration necessary for the normal functioning of the body cells is also intimately associated with sodium and chloride metabolism. Not only may sodium chloride depletion produce marked disturbances in the amount and distribution of body water, but the loss of either one of these ions without the loss of an equivalent amount of the other may cause serious disturbances in the acid-base balance of the body fluids.

1. *The role of sodium salts in the regulation of the hydrogen-ion concentration of the body fluids:* The near neutrality of the body fluids is preserved by the action of the various buffer systems and by the excretory and other activities of the lungs and kidneys. These buffer systems are made up almost entirely of certain weak acids and the sodium salts of these acids and include the carbonic acid-sodium bicarbonate combination, the mixture of the monosodium and disodium salts of phosphoric acid, and the sodium salts of the serum proteins. Normally the extracellular fluids contain about 1.3 mEq/L or 3 vols. per cent of free carbonic acid and 27 mEq/L or 60 vols. per cent of sodium bicarbonate, and as long as these proportions remain unchanged the pH of the body fluids is kept at its normal average of 7.4. Any acid which is formed in the body or introduced into it is immediately neutralized by reacting with the sodium bicarbonate of this buffer system, forming the neutral sodium salt of the new acid and free carbonic acid. The pH of the body fluids is therefore only slightly altered by the accumulation of acidic substances, and the mild increase in acidity associated with the higher concentration of free carbonic acid causes such an increase in the rate of excretion of carbon dioxide that the proportion of the free carbonic acid to the remaining sodium bicarbonate is maintained close to the normal ratio of 1 to 20.

Although in this way the action of the buffers succeeds in keeping the pH of the body fluids at normal values in spite of the constant production by the processes of normal metabolism of considerable quantities of acid, the amount of sodium bicarbonate available for future use is by this activity proportionately reduced. The capacity of the buffer systems would thus soon be exhausted were it not for the action of the kidneys. These organs are able to separate the sodium and acid ions and when necessary they can excrete a portion of the metabolic acids in the free form and eliminate a large part of the remainder as ammonium salts. The sodium with which these acids were combined in the blood stream is passed back into the body as sodium bicarbonate by the action of the renal tubules, and the buffer systems are in this way largely restored.

If instead of an excess of acidic substances there is a tendency (because of the ingestion of alkalies for therapeutic purposes or the persistent intake of an alkaline ash diet) towards an increase in the sodium bicarbonate of the body these mechanisms are reversed. Any increase in the blood bicarbonate is accompanied by a proportional increase in the free carbonic acid and the *p*H is but little changed. The kidneys cease almost entirely their production of ammonia, they excrete the metabolic acids as sodium salts, and if there is still an excess of base it is excreted in the form of the basic disodium salt of phosphoric acid and as sodium bicarbonate in an alkaline urine.

It is obvious then that the sodium salts play a very important part in this acid-base regulation and that it is essential for normal health that the sodium-bicarbonate content of the extracellular fluids be maintained within certain normal limits. In health this is accomplished simply by the action of the kidneys and by the ingestion in the normal diet of small amounts of sodium chloride. Most of this is excreted as common salt, but if there is any tendency towards increasing acidity the chloride ion is excreted as the ammonium salt and the sodium is retained as sodium bicarbonate. If, on the other hand, the trend is towards increasing alkalinity the acidic chloride ion is retained and the excess sodium is excreted in the urine.

The net result of all these activities is that in health the *p*H of blood and tissues is kept constant and the metabolic acids are excreted as they are formed, any excess base is excreted, and the blood bicarbonate (the alkali reserve or the CO_2 combining power) is kept at normal values.

2. *Disturbances in acid-base balance:* Although these mechanisms function almost perfectly in normal healthy people who are living on a normal diet, they may be considerably disturbed by a variety of abnormal and pathological conditions. The disturbances so produced give rise to the clinical picture of acidosis on the one hand and of alkalosis on the other.

(a) *Sodium depletion and acidosis:* If one excludes the relatively uncommon state of so-called respiratory acidosis, caused by an increased retention of carbon dioxide, the biochemical abnormality common to all conditions of acidosis is a deficiency in the amount of the blood sodium bicarbonate. The decrease may be large or small and the severity of the acidosis is indicated by the magnitude of the abnormality. In the more marked cases there is not only a decrease in the plasma sodium bicarbonate but an actual shift in the *p*H of the body fluids towards a more acid reaction, a condition which may be described as an uncompensated or only partially compensated acidosis.

The sodium bicarbonate of the body may be depleted in various ways. It may be used up in the process of neutralizing accumulated acids which may be formed in the body or ingested in amounts which are greater than can be excreted or destroyed. This is the reason for the acidosis of ketosis, of diabetes mellitus, and of hydrochloric acid or ammonium chloride medication, and it accounts in part at least for the acidosis of chronic nephritis and other conditions associated with renal insufficiency in which the ability of the kidney to excrete acidic substances is impaired. Sodium bicarbonate may also be depleted by excessive loss of fluid from the intestinal tract because the secretions of the pancreas, liver, and small intestine contain not only sodium chloride but small amounts of sodium bicarbonate as well. Such a loss depletes the blood and extracellular bicarbonate, lowers the alkali reserve, and produces an acidosis which may be as severe as any such state caused by an accumulation of acids and which is, in addition, nearly always accompanied by the consequences of a serious sodium chloride deficiency.

(b) *Chloride depletion and alkalosis:* The pathologic state opposite to acidosis is alkalosis and (again omitting the respiratory type, caused this time by excessive excretion of carbon dioxide) the characteristic biochemical finding in this condition, at the beginning at least, is an increase in the concentration of plasma bicarbonate and a mild to severe shift in the *p*H of the body fluids towards a more alkaline reaction. This state of affairs may of course be brought about by the excessive intake of alkalies, but a more important clinical variety is that which may be associated with the persistent vomiting of gastric juice containing normal or high concentrations of free hydrochloric acid. When chloride ion is lost in this form there is left behind an equivalent amount of sodium which immediately unites with the ever-present carbon dioxide to form sodium bicarbonate. In this way the plasma chloride is decreased, the plasma bicarbonate is increased, and an alkalosis is produced. Although the plasma sodium bicarbonate is increased in alkalotic states produced in this way, the total body sodium is likely to be seriously decreased. Not only is a small amount of sodium lost in the vomitus, but because of the alkalosis the kidney excretes sodium bicarbonate in the urine in an effort to lower the high concentration of this substance in the blood. In this way large amounts of base are lost and continue to be lost until the body refuses to sacrifice any more of its now badly depleted sodium stores in its effort to preserve the *p*H of blood within normal range. At this stage the urine will be acid in reaction even though the patient may be suffering from severe alkalosis.

WATER, SODIUM, POTASSIUM, AND CHLORINE DEFICIENCIES IN MAN

Many of the circumstances under which depletion of these important substances may occur have already been considered in the previous sections. No attempt will be made to discuss them individually for they are far too numerous and, indeed, no purpose would be served by so doing because the same broad general principles can be applied to all. In the case of each of these substances one should always consider the possibility of a deficiency state which may arise not only from an inadequate intake but also from uncompensated or excessive losses or from any combination of these two causal mechanisms.

As was pointed out by Kerpel-Fronius,[25] loss of water from the body without loss of salt produces one type of dehydration, whereas the loss of salt without corresponding water depletion produces a physiologic disturbance which is very different. Although the dehydration state most commonly encountered in clinical medicine is usually a mixture of these two types, not infrequently accompanied by acidosis or alkalosis (which has resulted from a loss of water, of salt, and of one or other of the individual ions), the severity of the individual deficiency present in any given patient will vary considerably from case to case. A correct assessment of the relative importance of the part played by each of these mechanisms in producing such dehydration can be made if the physician is familiar with the causes and manifestations of pure water depletion on the one hand and of pure salt depletion with or without acidosis or alkalosis on the other. If the physician can so assess the causes he will be able to prescribe the most effective therapy. If he cannot, it is probable that his therapy will be less effective than it should be and it may even do harm, for a state of water depletion will be made worse by the intravenous administration of normal saline just as the state of salt depletion will be aggravated by the administration of glucose in distilled water.

PURE WATER DEPLETION: WATER DEPRIVATION

Pure water depletion[32, 33, 36] is produced whenever the water content alone of the body is decreased without any accompanying significant loss of salt.

ETIOLOGY

The healthy person never suffers from water depletion caused by deficient intake except when, because of physical or geographical reasons, it is quite impossible for him to obtain water. The sensation of thirst is so strong that only the complete inability to obtain fluids will prevent its intake. Such circumstances are encountered of course by individuals who are lost at sea or in the desert or who are confined by accident or intention to a place where they cannot obtain or be given the necessary fluids. When no fluids at all are ingested the manifestations of water deprivation appear very rapidly because the constant and inevitable loss of water by the processes of evaporation and obligatory urinary excretion rapidly reduces the total body water to dangerously low levels. Even at relatively low temperatures these losses in an adult amount to at least 1500 cc. or about 2 per cent of the body weight daily. Although some sodium chloride is also lost at the same time, particularly if sweating is a feature, the salt loss is insignificantly small in comparison to the water loss and the clinical result is one of pure water depletion. As a water loss of 15 per cent of the body weight or 20-22 per cent of the body water is usually fatal, complete water starvation can be tolerated by adults even in temperate climates for little longer than a week or ten days. Infants, who lose water at a rate twice as great in proportion to their weight as that of adults, will survive for less than half this time under similar circumstances. If in either case exposure to high temperatures causes, in addition to the deprivation, an increased loss of water through the skin these periods may be considerably shortened.

Although the healthy person who is able to obtain all the water he desires never suffers from water deprivation, this is not true of individuals who may be sick or who have been injured. They may be unable to swallow fluids because of a local lesion in the throat such as quinzy or diphtheria, or in the esophagus such as cardiospasm, stricture, or carcinoma; or more commonly the desire for fluids may be so blunted by apathy, drowsiness, stupor, or coma, and the always present weakness may be so marked, that sufficient amounts of water are not taken voluntarily. Watchful care on the part of the attendants and the frequent offering of small amounts of liquids by mouth often persuades such patients to swallow the fluids necessary to keep them in water balance, but unless careful attention is paid to this aspect of treatment it is very likely that the problems of water depletion will be added to those of the primary illness.

Excessive losses of water are also common in illness, but as these are nearly always accompanied by salt loss, the picture produced is a mixed one and will be discussed later. The condition of pure water depletion is one which is caused in most instances by an inadequate intake of water. It may of course be aggravated by excessive losses and complicated by salt deficiency.

CLINICAL MANIFESTATIONS

The main clinical symptom of pure water depletion is thirst. This is marked and progressive but rarely intolerable. Salivary secretion is decreased and as a result the lips, tongue, and mucous membranes become dry and parched. The voice becomes husky, talking is difficult, and swallowing of dry food becomes impossible. If no water is taken, a loss of weight at a rate of 3 lb. or more daily occurs and this makes itself evident in a very short time by the sunken cheeks, ill appearance, decreased vitality, and increasing weakness of the patient. Vomiting is not a feature and any fluid which is taken in is kept down and is rapidly absorbed. Mild and then more severe mental changes eventually occur and finally the individual suffers from confusion and hallucinations. The actual cause of death, which in adults occurs after seven to ten days of complete water deprivation, is uncertain but it is believed[3, 25] to be due to the rising concentration of salt and of electrolytic osmotic pressure within the body fluids.

Soon after the beginning of the deprivation the urine volume is decreased sharply to 500-700 cc. per day and its specific gravity, providing that the renal concentrating power is normal, is elevated to 1030 or higher. Urine chlorides may be slightly increased or decreased but are not grossly abnormal.

In the early stages at least, there may be a mild increase in the plasma sodium and chloride levels. During this period there is no significant change in blood viscosity, serum proteins, or hematocrit reading, indicating that there is but little reduction in the blood volume. As a result the blood pressure and circulation are well maintained until just before death.

All these signs and symptoms agree with the conception described in a previous section that pure water deprivation results mainly in cellular dehydration. The inevitable minimal loss of water, which continues even though the intake has stopped, decreases the extracellular water and thereby increases the concentration of the extracellular electrolytes. The resulting rise in the electrolytic osmotic pressure attracts fluid from the cells in amounts which are sufficient to maintain the plasma volume and therefore to keep the circulation functioning in a normal way until the individual ultimately succumbs to the rising tonicity of all the body fluids.

PURE SALT DEPLETION: EXCESSIVE SALT LOSS

The condition of salt depletion[28, 33, 36, 43] is one which occurs whenever the total sodium chloride content of the body is decreased. In its pure form, which will be discussed in this section, it is caused nearly always by the inadequate replacement of excessive losses of salt, and as the sodium and chloride are lowered in approximately chemically equivalent amounts there is little disturbance in the acid-base balance. The manifestations are due entirely to the salt deficiency and to the extracellular desiccation and circulatory changes which are invariably associated with this depletion.

ETIOLOGY

Because of the widespread presence of salt in all normal foods and because of the efficient way in which the kidneys guard the body salt in the face of a threatened depletion, salt deficiency never occurs in healthy people unless significant losses are occurring from excessive sweating. Benedict[2] has shown by observations on his fasting patient that even the complete absence of all salt from the diet can be tolerated by humans for a considerable period. However, since salt is a constant constituent of visible sweat, considerable amounts of salt are lost whenever large quantities of sweat are formed. If no fluids of any kind are taken to compensate for such sweating the resulting condition is mainly one of water depletion because sweat contains more water and less salt than the body fluids. If, however, the thirst naturally caused by excessive sweating is assuaged by the drinking of water, and no attempt is made to replace the lost salt, the symptoms of water depletion are prevented but manifestations of sodium-chloride deficiency soon appear which may vary in severity from mild lassitude and weariness to the more serious and severe symptoms of so-called heat cramps, heat exhaustion, heat shock, and heat stroke.

Excessive sweating is of course common in the tropics where during the hot seasons as much as 10 or 12 liters of sweat containing 20-30 Gm. of salt may be lost daily. The losses are more marked among newcomers and the unacclimatized than they are among the native population and they are of course more exaggerated if much physical work, such as that necessarily carried out by the campaigning soldier, has to be done. The losses are particularly great among stokers and others who work in the high temperatures below decks in ships operating in tropical waters, and a graphic and complete description of the resulting clinical picture as it was seen in a number of the sailors of the Royal Navy during the Second

World War who did not consume their extra salt ration has been published by Stenning.[43]

Conditions equally conducive to sweating are also encountered in many of the industrial and other occupations of the temperate and colder zones, and these may cause the occurrence of salt deficiency states unless the salt intake of the worker is increased. The classic observations of Moss[35] upon excessive sweating were carried out on coal miners who worked in some of the deep hot pits of England. Workers in iron foundries, steel mills, paper mills, and boiler houses, as well as glass blowers, heat-treatment operators, limekiln workers, miners, and many others do their work in atmospheres that are often as hot and as humid as those to be found in the tropical jungles. Even the American woodsman who works outdoors in winter weather excretes, because of his very energetic occupation, large amounts of water and salt through his skin. The severe muscular cramps and other unpleasant results which may follow the drinking of copious quantities of ordinary water by foundry men, stokers, and others after a period of heavy work have long been known. Many of the symptoms thought previously to be due to exposure to excessive sunlight are undoubtedly due to salt depletion rather than to any intrinsically harmful effect of the heat itself, and it is quite likely that the "hot weather fatigue" so prevalent in the tropics and in other places during hot summer months is due to a mild salt depletion brought about in this way.

Severe sweating with consequent salt loss is also a characteristic symptom of febrile illnesses such as rheumatic fever, malaria, septicemia, advanced pulmonary tuberculosis, and many others. The excessive loss of sodium chloride in the urine, which continues even after the body salt has been reduced to low levels, is responsible for many of the manifestations of Addison's disease. Profound and severe losses of electrolyte are also occasioned by the excessive loss of any of the gastrointestinal secretions. In such cases the effect of the salt depletion itself is often much the most important feature, but they are frequently complicated by acidosis or alkalosis as well.

CLINICAL MANIFESTATIONS

General: In the patient with well-established salt depletion, thirst is not a prominent symptom as long as the water intake is adequate nor is dryness of the oral mucous membranes at all marked (unless the patient is a mouth breather). Anorexia and nausea are common and fluid and food given by the oral route may be vomited up almost immediately, causing further electrolyte depletion and exaggerating the condition. The main subjective symptom is a generalized weariness along with lassitude and loss of energy, and in addition there is definite muscular weakness so well exemplified by the marked asthenia of Addison's disease. Headache, giddiness, and a tendency to orthostatic fainting are noted in many cases.[33] Weight loss is considerable in spite of an adequate water intake and there is marked loss of interstitial fluid as evidenced by the sunken eyes, hollow cheeks, depressed temples, decreased cutaneous elasticity, and wrinkled skin, and in babies by the depressed fontanelles. In the more severe cases mental disturbances including confusion and delusions are not uncommon.

Muscle cramps: Painful muscle spasms, often called heat cramps, may occur in the calf muscles, abdominal muscles, the small muscles of the hand, or elsewhere[26, 43] and may involve particularly those muscles in active use at the time. They occur most frequently in workmen doing heavy labor in a hot atmosphere and are in these cases often precipitated by the drinking of large amounts of unsalted cold water.

Changes in the blood and circulation: When the salt depletion is severe there are obvious circulatory changes. The blood pressure may fall to very low levels and the pulse is feeble and fast. The extremities are cold, pale, and clammy and the superficial veins are collapsed. These are of course the symptoms and signs of clinical shock and marked salt depletion is thus one of the many causes of this syndrome. When the effects of salt depletion have reached this advanced stage, the resulting picture has been termed "electrolyte" shock [36] or "heat" shock.[43] All these manifestations have been shown to be due to the marked decrease in extracellular fluid and plasma volume which characterizes salt depletion. Decreases varying from 25 to 50 per cent have been reported[26, 30] and even greater losses may occur in the most severe cases. Marriott[33] expresses the view that definite evidence of circulatory disturbance will not become evident until the plasma volume has been reduced by about 15 per cent and that a systolic blood pressure below 90 mm. Hg probably indicates at least a 25 per cent reduction in plasma volume. As the decrease in blood volume in these cases is produced by the loss of water and salt only, the other constituents of the blood, such as the plasma proteins and the red blood cells, will be increased and there is on this account also an increase in the blood viscosity and specific gravity, findings which undoubtedly increase the circulatory embarrassment.

Examination of the blood shows a mild or moderate decrease in the concentration of the plasma sodium and chloride. The true severity of the salt loss may, however, be much greater than is indicated by these values, because a diminution in the total body salt usually leads to a decrease in the plasma volume rather than to any marked change in the concentration of these ions in the plasma.

There is also an increase in the level of the blood nonprotein nitrogen and urea, due in part at least to the inadequate excretion of urine caused by the fall in blood pressure and the resulting impairment of renal circulation.

Urine findings: The urine volumes are relatively normal at first and the specific gravities are not increased. A characteristic and helpful diagnostic finding is the near or complete absence of chloride from the urine except in the case of patients who have Addison's disease. If the condition increases in severity the amount of urine voided decreases with the decline in the blood pressure, and finally when this has fallen to 70–80 mm. Hg anuria occurs.

TABLE 25. COMPARISON OF EFFECTS OF WATER AND SALT DEPLETION*

Manifestation	*Pure water depletion*	*Pure salt depletion*
Dehydration	+ + + (cellular)	+ + + (extracellular)
Thirst	+ + +	absent
Lassitude	+	+ + +
Orthostatic fainting	absent till late	+ + +
Urine volume	scanty	normal till late
NaCl in urine	often +	always absent except in Addison's disease
Vomiting	absent	may be + + +
Cramps	absent	may be + + +
Plasma NaCl	slight increase or normal	diminished + + +
Plasma volume	normal till late	decreased + + +
Blood urea	+	+ + +
Hemoconcentration	not till late and slight	+ + +
Blood viscosity	normal till late	increased + + +
Blood pressure	normal till late	fall + + +
Water absorption	rapid	slow
Mode of death	? increased osmotic pressure	peripheral circulatory failure

* From Marriott[33]

COMPARATIVE EFFECTS OF WATER AND SALT DEPLETION

A useful comparison of the effects of water and of salt depletion is given by Marriott[33] in tabular form. This is reproduced in Table 25.

MIXED WATER AND SALT DEPLETION: ACIDOSIS AND ALKALOSIS

The two distinct pictures of water depletion and of salt depletion have been described at length in order to permit an understanding of the part which may be played by each of these causes in the dehydration of any given patient. Although at times these conditions are encountered in the pure form, the most frequent clinical type of dehydration is a mixture of the two varieties, which may or may not be accompanied by a disturbance in the acid-base balance.

ETIOLOGY

Many clinical conditions are characteristically accompanied by a great increase in the loss of both water and salt. One has only to think of the excessive sweating of fevers, the profuse vomiting of acute gastritis or pyloric obstruction, the severe diarrhea of gastrointestinal infection exemplified in its most serious form by the diarrheas of infancy and of Asiatic cholera, the large volumes of intestinal content that may be lost through an ileostomy, the marked increase in the urinary output of diabetes mellitus, diabetes insipidus, and chronic nephritis, the excessive loss of exudate from the surface of the skin after an extensive burn, the loss of sweat and blood that occurs during a serious operation, and the marked increase, due to accumulation of fluid, in the size of a traumatized limb, to realize how great these losses may be. If such losses are not corrected, severe clinical dehydration results.

If the disease process responsible for these losses is not accompanied by nausea or vomiting or any other condition which prevents an adequate oral intake, and if water and other unsalted fluids are freely taken by mouth, the end result will be one mainly of salt depletion. If, on the other hand, the abnormal losses are slight and the circumstances are such that a free intake of fluids and food by mouth is not possible the symptoms of water depletion are apt to be the more prominent. All variations between the two extremes may be encountered.

In addition to the manifestations of water and salt depletion, clinical dehydration is often accompanied by signs and symptoms of a disturbance in the acid-base balance. These occur because many of the causes of dehydration, such as diabetes and starvation, are associated with an increased production of metabolic acids and because many others lead to considerable losses of free acid or base from the body. In the latter group, as has been explained earlier, a depletion of chloride by vomiting frequently produces a state of alkalosis, and a depletion of sodium by diarrhea or other means produces an acidosis. Disturbances in the acid-base balance also occur in certain illnesses because of increased retention or excretion of carbon dioxide and, although these are uncommon and not often associated with serious dehydration, they are included in the following discussion for the sake of completeness and because of the difficulties which they may present, at times, in diagnosis.

The principal conditions which may be associated with acid-base disturbances are given in the following classification:

CLASSIFICATION OF ACID-BASE DISTURBANCES

ACIDOSIS

The state which exists whenever, because of an increase in body acid or a decrease in body base, the blood and extracellular tissues become, or tend to become, more acid in reaction.

1. *Respiratory Acidosis: Increased Plasma Carbonic Acid*
    - (a) Conditions in which there is interference with the excretion of CO_2:
        - Pulmonary and cardiac disease
        - Anesthesia
        - Asphyxial states
    - (b) Breathing in an atmosphere containing excessive quantities of CO_2
2. *Metabolic Acidosis: Depletion of Plasma Sodium Bicarbonate*
    - (a) Accumulation of nonvolatile acids
        - Medication with HCl, NH_4Cl, ammonium mandelate, etc.
        - Increased production of metabolic acids:
            - Diabetes mellitus
            - Starvation
            - Cyclic vomiting of children
            - Pernicious vomiting of pregnancy
        - Decreased excretion of metabolic acids:
            - Chronic nephritis and other urinary tract lesions
    - (b) Excessive loss of sodium bicarbonate:
        - Diarrhea
        - Losses through intestinal fistulas

ALKALOSIS

The state which exists whenever, because of a loss of body acid or an increase in body base, the blood and extracellular tissues become, or tend to become, more alkaline in reaction.

1. *Respiratory Alkalosis: Depletion of Plasma Carbonic Acid*
    - Over-breathing
        - Hysteria
        - Certain cases of encephalitis
        - Anoxic anoxemia
2. *Metabolic Alkalosis: Increased Plasma Sodium Bicarbonate*
    - Increased intake of alkalies
    - Increased loss of hydrochloric acid

It should be remembered that in conditions associated with nausea and vomiting there is also a degree of starvation because of the impaired ability to take in food or to retain it. If the vomiting is severe and the gastric juice contains large quantities of free hydrochloric acid it is likely that the resulting disturbance in the acid-base balance will be one of alkalosis. On the other hand, if the nausea and the consequent anorexia are marked and the vomiting is mild, or if the gastric juice contains very little or no free hydrochloric acid, it is probable that acidosis due to starvation rather than alkalosis will be produced. In cases of diarrhea the original acidosis caused by excessive excretion of sodium may be aggravated by impaired renal function associated with the dehydration and by a degree of starvation ketosis as well.

CLINICAL MANIFESTATIONS OF ACIDOSIS AND ALKALOSIS

Respiratory acidosis: Because carbon dioxide diffuses out of the blood into the alveolar spaces many times more rapidly than oxygen passes in, it is likely that patients with respiratory or cardiac disease or any other condition which might interfere with the excretion of CO_2 will exhibit manifestations of anoxemia such as cyanosis and dyspnea long before they have any serious retention of carbon dioxide. The marked exaggeration of the dyspnea on effort may, however, be due in part to CO_2 retention. It is probable, too, that in the asphyxial states the symptoms of anoxemia will be the more prominent. On the other hand, CO_2 accumulation caused by inhalation of a carbon-dioxide-rich atmosphere increases the depth and rate of the respirations, and anoxemia is therefore not a feature unless the oxygen content of the air being breathed is low. In both cases there is an increase in the plasma sodium bicarbonate (at the expense of the plasma chloride, which falls) in order to compensate for the presence of the larger amount of free H_2CO_3. In this they resemble cases of metabolic alkalosis, a fact which should be remembered when considering the differential diagnosis of the causes of an elevated plasma bicarbonate. They can be distinguished chemically by a determination of the blood *p*H, which is lowered in cases of respiratory acidosis and elevated above normal in patients with metabolic alkalosis.

Metabolic acidosis: The chief clinical manifestation of metabolic acidosis is hyperpnea, and the severity of this provides a good index of the degree of the acidosis except in premature and newborn infants and in patients suffering from shock.[7] The other clinical findings will depend to a large degree upon the cause of the acidosis and upon the extent of the salt or water depletion which is associated with it. The urine will be acid in the absence of alkalinizing urinary tract infections, will contain large amounts of sugar and ketone bodies in diabetic acidosis and considerable amounts of ketone bodies in any case in which starvation is a feature, and will show the characteristics of chronic nephritis or other kidney disease if some renal condition is responsible for the acidosis. In all these there will be a decrease in the plasma sodium bicarbonate from the normal value of 55–65 vols. per cent to as low as 10 vols. per cent in the extreme cases. When respiratory alkalosis can be ruled out, the finding of a low plasma bicarbonate is proof that a metabolic acidosis is present.

Respiratory alkalosis: This condition appears as the result of marked hyperventilation, which may be produced voluntarily or which may be found in hysteria, in certain cases of encephalitis, and in patients who are suffering from anoxic anoxemia. If the alkalosis is severe, signs of tetany with Chvostek's sign, Trousseau's sign, carpopedal spasm, and vocal stridor may be present. The excessive excretion of CO_2 which occurs in this type of alkalosis is in part compensated for by a decrease in the plasma bicarbonate, and for this reason care sometimes has to be taken to distinguish it from cases of metabolic acidosis who also have hyperventilation and a low plasma bicarbonate.

Metabolic alkalosis: This type of alkalosis may appear as the result of an excessive and prolonged intake of alkalies, particularly sodium bicarbonate, as a therapeutic measure; or it may result as explained above from persistent vomiting of gastric juice containing large quantities of free hydrochloric acid. The latter group is always accompanied by serious clinical dehydration and other evidence of water and salt depletion. Such alkalosis is frequently associated with shallow and irregular respirations, and in severe cases there may be evidence of increased irritability of the neuromuscular system. The urine is at first usually alkaline but in the later stages of the illness, when the sodium stores have been depleted, the urine becomes acid in reaction as the kidneys endeavor to conserve the rapidly diminishing supply of body base. Examination of the blood shows a marked fall in the plasma chlorides, which in severe cases may fall to less than half the normal value of 340-370 mg. per cent, and, along with this decrease in the chlorides there is a characteristic increase in the plasma bicarbonate which may rise to 100 or even 110 vols. per cent.

Potassium Deficiency

Potassium is the principal cation of the fluid within the tissue cells, where it probably plays a part similar to that of sodium in the extracellular fluid. It has other functions, however, than merely to regulate the osmotic pressure of the intracellular fluid, functions which are related to neuromuscular transmission of nerve impulses, to muscular contraction, to the processes of phosphorylation and the deposition of glycogen, and to still others which as yet are not well understood.[16]

Although most of the potassium is within the cells, a small and fairly constant quantity is present in the blood plasma in an amount which varies from 13.5 to 21.5 mg. per cent or 3.5 to 5.5 *mEq/L.* Any marked variation from this normal range results in definite disturbances in the functions of muscles and nerves. In health the normal blood levels are maintained, in spite of wide variations in the potassium intake, largely through the regulatory activity of the kidneys.

ETIOLOGY

Because potassium is a very essential constituent of cellular protoplasm, an adequate supply of this element is obviously necessary for growth and for cellular maintenance. However, because of the universal presence of large amounts of potassium in all ordinary food and because of the relatively small amounts required, the intake of this substance in health is never so inadequate that it leads to clinical manifestations of deficiency. Evidence of potassium deficiency is only encountered as a result of the excessive losses which occur in certain types of illness and also in the rare condition of familial periodic paralysis.

It has previously been stated that the cell membranes of living tissues are relatively impermeable to sodium and potassium ions. Whether or not such a simple explanation has any value, there is some natural force which under ordinary circumstances keeps the potassium inside the cells and the sodium outside in the extracellular fluids. When the cell is injured and the protoplasm within it is broken down the potassium is liberated and passes out of the cell into the general circulation from which it is largely excreted by the kidneys. In starvation, fever, and other conditions which lead to excessive destruction of body protein, potassium, phosphorus, and nitrogen are all excreted in the urine in proportions which are similar to those found in the tissues.

It has, however, now been established that under certain circumstances the cell membrane does allow potassium to leave and sodium to enter the living cell in relatively large amounts.[10, 11, 19] Much of this potassium lost from the cells is excreted in the urine and stools and if the loss so produced is at all large, serious potassium depletion may occur. When the conditions which have led to the loss of potassium are overcome this ion will, if available, once more return to the cellular compartment and in this way the plasma potassium level may be markedly decreased. If adequate potassium is not present in the body to supply the cellular needs under such circumstances, a full correction of the electrolyte and acid-base disturbance will not be possible until the necessary potassium is made available from some outside source. If oral feeding can be resumed, the potassium deficiency will be rapidly remedied because of the high content of potassium in ordinary foods; but if this is not possible and it is necessary to carry on with intravenous alimentation, the possibility that it may be necessary to supply a small amount of potassium should always be borne in mind.

Depletion of cellular potassium has been produced experimentally in animals by long-continued ingestion of diets low in potassium. In humans important losses of cellular potassium have been shown to take place as the result of trauma, shock, hemorrhage, severe diarrhea, sprue, diabetic coma, and severe alkalosis due to chloride loss or associated with Cushing's syndrome. Loss of intracellular potassium in excess of that to be expected from protein breakdown is a general response to water depletion from any cause.[14]

CLINICAL MANIFESTATIONS

The most obvious manifestation of low plasma potassium is muscular weakness, which is sometimes so marked that it amounts to complete paralysis. This is seen typically in patients who have the rare disease known as familial periodic paralysis, of which the etiology is unknown, and the paralysis can often be brought on in these patients by any procedure (such as the administration of insulin) which tends to lower the plasma potassium.

Marked muscular weakness also occasionally appears in patients with diabetic coma soon after the institution of vigorous therapy with insulin, glucose, and normal saline.[18, 24, 34, 37] In addition to the generalized skeletal muscle weakness seen in these patients, certain cardiac disturbances may also occur, including tachycardia, arrhythmia, ventricular dilatation, murmurs, and electrocardiographic abnormalities indicating that the heart muscle may be involved as well. Similar attacks of transient muscle paralysis have also been described[45] in patients with Addison's disease following the administration of desoxycorticosterone and intravenous saline solutions, and in two cases of chronic nephritis.[5] These signs and symptoms have all occurred at a time when the serum potassium level was found to be low, and they were all improved by the administration of small amounts of potassium salts.

Although the cellular potassium is depleted in patients with diabetic coma or severe diarrhea, the concentration of this ion in the serum prior to treatment is apt to be normal or even higher than normal. It is only after treatment has been started that the concentration of the potassium in the serum of patients with diabetic acidosis has been noted to drop to very low levels (6.9 mg. per cent or 1.8 *mEq/L* in Frenkel's case[18] and below 2.5 *mEq/L* in others) and it is only at this time, when the serum potassium levels are so depressed, presumably as a result of a rapid shift of potassium from the extracellular to the cellular phase, that the above symptoms of potassium deficiency have appeared. In cases of severe infantile diarrhea a decrease in muscle tone is always found, but actual paralysis has not been observed, although "after treatment with sodium and chloride such an occurrence is a possibility."[11]

SHOCK

Shock is the term used to describe the state of severe generalized disturbance of body functions which may follow any injury, severe infection, dehydration, or other serious insult to the living individual. The condition has usually been divided into primary and secondary phases according to the time of onset, but such a division is probably undesirable because the time relationships are of little value in helping to assess the nature and severity of shock in any given person. The term "primary shock" should be abandoned[4] and the type of shock expressed, regardless of the time of onset, in terms which indicate its physiologic etiology.

ETIOLOGY AND CLASSIFICATION

Shock has been defined by Peters[39] as "any condition in which the volume of the circulating blood is too small in proportion to the size of the vascular bed." He of course points out that this definition embodies a fallacy, for "in any elastic system filled with fluid the volume of fluid must always equal the volume of the system in which it moves." It is obvious, however, that any diminution in the volume of the fluid inside such a *distended* elastic system will, if there are no compensatory mechanisms, cause a lowering of the pressure exerted by this fluid even though the system remains completely filled (just as the pressure within an automobile tire is reduced by releasing some of the air); and any relaxation of the tension exerted upon the contents by the walls of such a system will similarly lead to a fall in the internal pressure. In the case of the arterial tree a moderate decrease in the blood volume can occur without a fall in blood pressure because of the compensatory contraction of the peripheral arterioles. When this counteracting mechanism is inadequate to compensate for larger losses of blood volume, the blood pressure will fall below normal values; and when the capacity of the vascular bed is increased or the resistance to the outflow of blood is diminished by a relaxation of the tone of the peripheral arterioles there will also be a fall in the arterial blood pressure. As a result of this fall in pressure the flow of blood to the tissues is decreased, the nutrition and function of vital organs such as the brain, kidneys, heart, and even the blood vessels themselves is impaired, and disturbances are thus produced which are recognized as the symptoms of "shock."

If this conception of shock is accepted then it is obvious that there are many conditions which may cause its appearance. The volume of the blood within the arterial tree may be lowered by external or internal hemorrhage, by the loss of plasma into injured areas or into the surface lesions of burns, by the loss of water and electrolyte to the exterior or into traumatized tissue or into the interstitial spaces because of a generalized capillary injury, or by a sudden diminution in the cardiac output such as may be produced by vagal stimulation or by a coronary thrombosis; or the volume of the space in which the circulating blood is confined may be enlarged because of relaxation of arterioles or dilatation of capillaries from neurologic or toxic causes.

Shock may then be classified on an etiologic basis as follows (modified after Blalock):[4]

CLASSIFICATION OF SHOCK

1. *Neurogenic Shock*
   Synonymous with "primary" shock, syncope, or fainting, probably caused by reflex vascular dilatation and slowing of the heart through the vagus; may be caused by fright, fear, pain, or similar stimuli. Usually not serious and of short duration.
2. *Oligemic Shock: Decreased Blood Volume*
   - (a) Loss of whole blood: external or internal hemorrhage.
   - (b) Loss of plasma: burns, crushing injury.
   - (c) Loss of water and electrolyte: vomiting, diarrhea, diuresis, excessive sweating, etc.
3. *Vasogenic Shock.*
   Vascular dilatation due to toxic causes such as histamine which act directly upon the walls of the blood vessels.
4. *Cardiogenic Shock.*
   Diminished cardiac output because of causes which are primarily cardiac.
5. *Pneumogenic Shock.*
   Fat embolism, pulmonary embolism.

CLINICAL MANIFESTATIONS

This is no place to discuss all the varieties of shock or all the controversial theories regarding its causation. However, from what has been said previously it will be recalled that a reduction of blood volume is one of the consequences of salt depletion. For this reason all the clinical conditions which are associated with loss of salt may lead to a state of oligemic shock which may be just as severe and serious as any of the similar states caused by hemorrhage or trauma.

The cardinal manifestations[44] exhibited by a patient in fully developed oligemic shock of this kind include extreme weakness, a cold clammy skin, an ashen grey cyanotic pallor, a rapid and almost imperceptible pulse, a subnormal body temperature, oliguria or anuria, and a systolic blood pressure which is definitely below normal and sometimes quite unobtainable. This clinical picture with its characteristic symptoms and signs is readily enough recognized, but the response to treatment when the condition is so far advanced is often very poor.

The typical picture of oligemic shock just described does not appear at once but takes a varying time for its development. During this period symptoms and signs usually become obvious which indicate that the sequence of events that will sooner or later lead to its occurrence have been initiated. In "heat shock" due to excessive loss of salt by sweating, a prodromal stage of some days of tiredness, lassitude, weakness, dizziness, nausea, and headache often precedes the more obvious signs of typical shock[43] and a similar prodromal stage, accompanied by restlessness, cold sweats, increasing pulse rate, decreasing pulse volume, and falling blood pressure precedes the state of frank shock which may be produced by any of the clinical conditions causing excessive salt losses. In wound shock caused by hemorrhage or trauma and aggravated frequently by dehydration, fatigue, fear, infection, and other factors, there is usually a similar important period after the time of injury during which, even though the patient's condition seems to be excellent, similar symptoms and signs are obvious to the careful observer and indicate the need for immediate therapy.

When the decrease in blood volume causing shock is due to loss of plasma or of water and electrolyte, the red cells of the blood become more concentrated, as is shown by an increase in the cell count, hematocrit value, hemoglobin, viscosity, and specific gravity. When only water and electrolyte are lost as in salt depletion, not only the red cells but the plasma proteins as well will be increased in amount. Single determinations of any of these blood constituents are of little value, but serial estimations are of some help as they will indicate the nature of any change that is taking place.

Prevention of Water and Electrolyte Deficiencies

PREVENTION OF DEFICIENCIES IN NORMAL PEOPLE

In temperate climates healthy children and adults take in, of their own accord, more than enough water and salt to meet their requirements and there is no need to be concerned about the possibility of deficiency. Care should be taken, however, that infants and others who are not able to help themselves are supplied with the necessary amount of fluids. It is the practice among Canadian physicians to allow infants 2½–3 oz. fluid per pound of body weight each day (up to a total of 40 oz.) in their regular formula[46] and in addition the baby should be offered halfway between feedings as much plain boiled water as he wishes to take. It is very important, particularly during the hot weather, that adequate amounts of fluid are given to the small infant. As most of the fluid taken in will be milk or prepared with milk the intake of salts will be fully adequate to meet all the normal sodium, potassium, and chloride needs.

When the conditions are such that there is excessive sweating it may be necessary to take steps to make certain that an adequate amount of water and salt is consumed even by adults. The symptom of thirst usually encourages the intake of sufficient fluids but water should always be made freely available. Infants and other helpless people again need special care in this respect. Salt depletion is even more likely to occur from sweating and it is responsible for much of the "hot weather fatigue" and other similar symptoms so common among those who live in the tropics or who work at hot occupations. In order to prevent the occurrence of this deficiency, salt tablets are now available to the workmen in many factories, especially during the hot weather. The salt is dispensed as 10-grain tablets from a special container near a drinking water supply and the workers help themselves. In Ontario, workers exposed to hot conditions are advised to take, along with all the water they desire, five or six ten-grain tablets daily if they are engaged in light to medium work, eight to ten tablets daily if their work is heavy, and twelve to fifteen such tablets (a total daily intake of eight to ten Gm.) if their work is unusually heavy.[8] In the sweltering heat of the tropics an even higher intake may be desirable, particularly in the case of soldiers, sailors, and others who have to labor strenuously.[26, 43]

PREVENTION OF SALT AND WATER DEFICIENCIES AMONG THE SICK

It is even more essential that the already sick patient be given his full normal fluid requirement (see Table 22) and more if he is febrile or losing excessive amounts in any way. If foods and fluids can be taken and retained by the oral route, there will be no need to use any other means of administration, and the frequent offering of small amounts of fluids and of liquid, semi-liquid, or soft foods such as fruit juices, milk, soft drinks, broths and soups, water itself, jellies, custards, and so on, will do much to ensure an adequate intake not only of water but also of salt. A careful clinical record of all the fluid and food taken, of vomitus, diarrhea, and other abnormal losses, and of all the urine passed, must be kept, and it should be summarized every eight to twelve hours, or more frequently when necessary for the guidance of the physician. One should be satisfied only if, on such a regimen, the intake is sufficient not only to meet the individual's normal requirements but also to compensate for all abnormal losses. Evidence that the intake is adequate will be furnished by the absence of any clinical evidence of dehydration and by the output of a normal quantity of urine, always remembering that patients who have any renal insufficiency may have to excrete twice the normal volume or more in order to prevent retention of waste products. If there are no extra salt losses, no salt in addition to that contained in the food and used for seasoning need be added, but if there is much loss of intestinal fluid from diarrhea or other cause, extra salt in amounts equivalent to that lost (the intestinal fluid being considered to have a salt content equivalent to that of normal saline) should be administered.

If, however, the patient is unable to take in or to retain the requisite amount of food, water, and salt by mouth, these will have to be administered parenterally by the intravenous or subcutaneous route. The amount and quality of the fluids to be administered in this way should be calculated as carefully as possible and, as Darrow[10] has emphasized, each patient must be treated as an individual problem and according to the nature of the clinical disturbance. Such parenteral alimentation, to be ideal in the case of a patient who is not able to take anything by mouth, should include the necessary fluids, electrolytes, calories, protein, and essential food factors. However, when it is to be continued for a short period only it need not supply more than the necessary water and salt along with glucose in amounts sufficient to supply a part of the caloric requirement and to prevent ketosis and excessive protein breakdown. When necessary, the calories and protein requirement can be met by the addition of the calculated amounts of glucose and amino acids, and the water-soluble vitamins as well may be added directly to the mixture.

As far as the fluid and electrolyte are concerned, the problem is to furnish in a satisfactory form enough of both to meet the requirement and to compensate for losses. It must be remembered that normal saline contains far too much sodium chloride to permit it to be used as the sole source of fluid for normal maintenance. The daily water allowance of a 5 Kg. infant calculated on the basis of 150 cc. per Kg. is 750 cc. If this were all given as normal saline, the salt administered with this fluid would amount to 6 Gm., or six times the normal salt allowance of 1 Gm. daily[6] for an individual of this size. In such an instance the salt requirement will be met by approximately 125 cc. of normal saline and the remainder of the water requirement should be supplied in the form of 5 or 10 per cent glucose solution which should be mixed with the salt solution prior to its administration.

Similarly, the necessary salt for the daily needs of a 70 Kg. adult (i.e., 6 Gm.)[6] will be contained in 700 cc. of normal saline, and to this there should be added enough 5 or 10 per cent glucose to make up the total fluid requirement (in this case about 2800 cc. per day at 40 cc. per Kg.).

The Treatment of Established Water and Salt Deficiencies

A state of dehydration with or without the added complications of acidosis, alkalosis, or shock is already established in many sick patients by the time they are seen by the physician. In such cases immediate vigorous treatment of the dehydration is of first importance and is often even more essential than the treatment of the disease which caused its appearance. If the disease is a medical condition such as diabetic coma or acute diarrhea, the treatment of the dehydration and acidosis goes hand in hand with the specific measures adopted to control the primary cause. If the condition is one such as intestinal obstruction which has to be dealt with surgically, complete relief of the dehydration with restoration of the water and salt deficiencies must be obtained before the necessary surgery can be carried out with safety.

DIAGNOSIS

Before adequate treatment can be prescribed for such patients it is of course necessary that an accurate diagnosis of the nature and degree of the depletion be made, and this can be done only by a careful appraisal of the condition of the patient by means of a consideration of the clinical history and physical examination, and at times by the results of certain laboratory tests.

1. *History and Physical Examination:* An alert appreciation of the conditions in which such deficiencies are likely to occur, and an awareness of the possibility that they may develop, frequently permit one to anticipate their appearance and to be specifically on the watch for them. An accurate knowledge of the patient's history is important, for it not only permits a moderately accurate estimation of the severity of the water and salt losses and of the extent of the starvation but also suggests whether or not the dehydration is likely to be accompanied by acidosis or alkalosis. Attention should be paid to the nature and duration of the illness, the extent of the weight loss, the food and fluid intake, the approximate amount of fluid lost by vomiting, diarrhea, in the urine, and by other means, and to the presence of fever, sweating, and other disturbances. A complete physical examination, noting especially the appearance of loss of weight, the evidence of drowsiness or toxicity, the moistness of the tongue and mucous membranes, the tension of the eyeballs, the elasticity and turgor of the skin and subcutaneous tissues, and in babies the level of the fontanelles, will indicate the severity of the dehydration

at the time of the examination. An air-hunger type of respiration suggests a metabolic acidosis, or very rarely a respiratory alkalosis due primarily to over-breathing. Alkalosis is suggested by shallow slow irregular respirations which, as Drake[13] has emphasized, may be obvious in infants only when they are lying quiet and undisturbed. Hyperactive reflexes and other signs of alkalotic tetany are but rarely encountered and then only in the severest cases. The odor of acetone is readily detected on the breath of patients who have definite ketosis. Cold sweats, low blood pressure, greyish pallor, and a pulse that is feeble and faster than would be expected from the patient's age and temperature suggest that there is a significant decrease in the blood volume and that shock is present or imminent. Any unusual muscular weakness or unexplained paralysis should suggest the possibility of a potassium deficiency.

2. *Urine Examination:* Examination of the urine also yields very valuable information. The volume will be low* and the specific gravities high in patients who have significant water depletion; and the absence or near absence of chlorides from the urine is good evidence of salt deficiency. Urinary chloride can be estimated simply by the Mohr method which has been adapted to clinical use by Fantus[15] and also used extensively by Marriott.[33] The determination is carried out as follows:

SIMPLE, ROUGHLY QUANTITATIVE TEST FOR CHLORIDE IN URINE

Place 10 drops of urine delivered from a pipette in a small test tube and to it add 1 drop of 20 per cent potassium chromate solution. Rinse the pipette free from urine with distilled water and once with a small quantity of 2.9 per cent silver nitrate solution. Using this same pipette (or one delivering the same size of drop) add to the urine mixture with shaking and drop by drop the 2.9 per cent solution of silver nitrate until a permanent change in the color from yellow to red brown occurs. The number of drops of silver solution used in this titration gives the approximate chloride content (as sodium chloride) of the urine in grams per liter; i.e., if 5 drops of the silver nitrate solution were used, the chloride content of the urine would be 5 Gm. per L. (as NaCl). If the color change takes place with the first drop, chloride should be regarded as absent, a finding which indicates salt depletion unless the test has been carried out during a period of marked diuresis.

Any other method of chloride analysis may of course be employed, such as the very simple one of Schales and Schales[40] modified if necessary for urines of low chloride content or high alkalinity as suggested by Asper, Schales, and Schales.[1] Stenning[43] simply adds 5 drops conc. HNO_3 and 5 drops of 1 per cent $AgNO_3$ to 5 cc. urine and notes the nature and density of the precipitate. With chloride concentrations of 5 Gm. per L.

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* See Table 22 (p. 336) for normal values at different ages.

or more a dense curdy white precipitate forms immediately. With smaller amounts the density of the precipitate decreases until in the complete absence of chloride no precipitate at all appears.

In urines with a specific gravity of more than 1020 a chloride content of less than 3 Gm. per L. suggests chloride depletion, but if 5 Gm. per L. or more are present salt depletion is unlikely unless the patient has Addison's disease or is being given intravenous saline.[33]

Ketone bodies can be readily detected by the sodium nitro prusside test for acetone and by the ferric chloride reaction for diacetic acid. Care should be taken in diagnosing acidosis or alkalosis from the reaction of the urine, for, as indicated previously, the urine may be alkaline in acidosis because of a urinary tract infection or acid in alkalosis because of a marked depletion of body base.

3. *Blood Examination*: Determination of the packed cell volume or hematocrit value of the blood, or of its hemoglobin or serum protein content, viscosity, or specific gravity may give helpful information about the degree of hemoconcentration and of fluid and electrolyte loss. It should be stressed, however, that no single isolated estimation of this kind is of much use because of lack of knowledge of what these values were before the onset of the illness. Serial determinations of these characteristics during treatment will be of considerable help in evaluating the response to therapy.

Determination of plasma chloride may indicate the presence of a chloride deficiency, and an estimation of the plasma bicarbonate will show whether or not there is significant acidosis or alkalosis. In this connection it will be recalled that in the rare respiratory forms of acid-base disturbances, the plasma bicarbonate is, contrary to the findings in the more common and more important metabolic varieties, elevated in acidosis and depressed in alkalosis and for this reason a determination of the blood *p*H may be necessary if one has to distinguish between otherwise doubtful cases by chemical means alone.

Determination of the total base or of sodium or other electrolyte in the blood fails to give a true idea of the extent of the deficiency in a salt-depleted person. The reason is of course that in such patients the *volume* of the blood and extracellular fluids may be markedly decreased even though *concentration* of electrolyte in these fluids is relatively normal. More information would be gained if such determination were combined at the same time with an estimation of the blood and extracellular fluid volumes. However, these are not simple procedures and are particularly fraught with difficulties in those patients with severely depleted blood volume, shock, and impaired circulation, where conceivably they would yield the most information.

TREATMENT

Having determined as accurately as possible the nature and extent of the water and salt depletion, the physician must prescribe the proper therapy. If the patient is not too severely dehydrated, is not nauseated or vomiting, and is able to swallow and to retain fluids, it will likely be possible, by the frequent oral administration of small amounts of water, fruit juices, glucose drinks, broths and other similar liquids, to overcome the dehydration. If, however, the depletion is more than moderately severe and if, as so often happens, nausea and vomiting or other conditions preclude the administration of anything by mouth, the fluids and electrolyte must be administered by the intravenous or subcutaneous route; and this should if possible be done in a hospital or similar institution where a continuous record can be made not only of the medication but of the patient's general condition and his response to treatment.

1. *Solutions to be Used:* The composition of the fluid administered will depend upon whether the dehydration has been caused largely by water deprivation or from the excessive loss of electrolyte-containing body fluids, and also upon whether or not there is significant acidosis or alkalosis. The amount which should be given and the rate at which it should be administered will be determined by the age and size of the patient, the severity of his deficiency, and the way he reacts to its administration.

If the dehydration has been caused almost entirely by water depletion and there has been no abnormal loss of salt, it will be obvious that the patient requires much water and little sodium chloride. These needs cannot be supplied by the use of normal saline because the infusion of the necessary amount of water in this form will lead at the same time to the administration of excessively large amounts of salt and will therefore do little to relieve the condition. This is well illustrated by a discussion of a hypothetical case by McCance and Young[32] who say: "Let us suppose that a patient is unable to take anything by mouth and that, in consequence, he is given, during 24 hours, 1500 cm.^{3} of normal saline intravenously, i.e., 1500 cm.^{3} of water and 15 g. of salt. He will require 1000 cm.^{3} of this water to make good the unavoidable losses from his lungs and skin and so his kidneys will have the impossible task of excreting 15 g. of salt in 500 cm.^{3} water. The kidneys may excrete most of the 15 g. of salt but they can do so only by drawing upon water which was already in the body. Hence the administration of 1500 cm.^{3} of normal saline could only make the patient more dehydrated."

Treatment of dehydration of this kind can best be carried out, if the oral route is not possible, by the intravenous administration of 5 or 10 per cent glucose in ⅓-or ¼-strength normal saline. These solutions supply not only fluid but also the glucose necessary to relieve the starvation ketosis and to decrease the breakdown of body protein. Such a mixture is particularly useful in the treatment of dehydration of babies[13] who are less able than adults to deal with relatively large amounts of salt.

When, however, the dehydration is one that has been caused by excessive loss of body fluids containing sodium chloride and other electrolytes, it is not only desirable but absolutely essential that the salt as well as the water be replaced. This can be most easily accomplished by the intravenous injection of normal saline, with or without glucose, which supplies both water and salt in concentrations which are not grossly dissimilar to those present in the lost body fluids. Even in pure salt depletion, such as that which follows excessive sweating and the drinking of copious quantities of unsalted liquids, normal saline will be an adequate fluid, for the salt will be retained and the excessive water will be rapidly excreted by the kidneys.

The administration of isotonic saline will do much to restore the lowered blood volume of patients who are badly depleted of salt, but in those cases in which there is imminent or manifest oligemic shock it is probably advisable to supplement the salt solutions by transfusions of plasma (if there is evidence of hemoconcentration) or of whole blood. When shock has been caused by hemorrhage or plasma loss, whole blood or plasma, as the case may be, must of course be given.

If alkalosis is present, physiologic saline in 5 or 10 per cent glucose is almost the ideal fluid to use, as it not only corrects the hypochloremia but also elevates the serum sodium to a point where the body is permitted to improve the alkalosis by excreting a portion of the excess plasma bicarbonate in the urine.

When acidosis is a complication, normal saline will, in the presence of normal renal function, again be suitable in most cases. The kidneys, by retaining the sodium ion and excreting the chloride ion (as the ammonium salt), will bring about in these patients an increase in the plasma sodium bicarbonate and thus correct the acidosis. In some of the more serious cases, however, there is at times a distinct impairment of kidney function which may make it necessary to supply not only sodium chloride but also sodium bicarbonate or sodium lactate (which is changed in the body to sodium bicarbonate). To this end one may give either a mixture made up of 2 parts normal saline and 1 part seventh-molar sodium bicarbonate (1.2 per cent $NaHCO_3$) or seventh-molar sodium lactate, as recommended by Butler and Talbot,[7] or the Lactate Ringer solution of Hartmann[23] (NaCl 6 Gm., sodium lactate 2.7 Gm., KCl 0.4 Gm., and $CaCl_2$ 0.2 Gm. per L.). These mixtures should be given until the hyperpnea and other signs of acidosis have distinctly improved, and when this has been accomplished the fluid may be replaced by normal saline.

In children the acidosis and dehydration of severe diarrhea is accompanied by considerable potassium loss.[11] Because of this, Govan and Darrow[22] have used for the treatment of such patients a potassium-containing solution (NaCl 4.4 Gm., KCl 2.7 Gm., sodium lactate 6.0 Gm. per L., now available as Darrow's Solution) with the result that there has been a considerable improvement in the infant mortality of this condition.[22, 46] This solution can be given subcutaneously without modification, but for intravenous use it should be diluted with two or three parts of 5 or 10 per cent glucose. Potassium in the form of the chloride has also been given with considerable benefit to patients who during recovery from diabetic acidosis or coma have exhibited signs of potassium deficiency.[18, 24, 34, 37] Care has to be taken when administering a potassium salt to avoid giving too much or giving it too quickly because symptoms of potassium poisoning, notably heart block, often appear[17] if the serum concentration of this ion is raised above 10 mEq/L (39 mg. per cent) a value which is little more than twice the normal. The danger is small if the salt is given by mouth and there is normal renal function, but if it is given intravenously at too rapid a rate or if there is impairment of renal excretion, an accumulation beyond safe limits may easily occur. Govan and Darrow[22] advise that the dose of their solution given to infants should not be more than 80 cc. (containing 0.22 Gm. KCl) per Kg., that it should be given slowly by hypodermoclysis over the space of 4 to 8 hours or more, and that it should not be used until shock and oliguria (if present) have first been at least partially overcome by the use of saline and glucose solutions. In the case of adults, treatment with potassium should probably be restricted to those patients who are considered to be showing early evidence of potassium deficiency and even with these should be postponed if possible until urine is being freely excreted. The potassium as potassium chloride should be given to these patients by mouth or subcutaneously, rather than intravenously, at a rate no more rapid than 0.5 to 1.0 Gm. per hour and the total dose should probably not exceed 5 Gm. Careful watch, including the use of electrocardiograms, should be kept for the development of the signs of potassium poisoning and the medication should be stopped immediately if any evidence of intoxication is discovered or as soon as the symptoms of potassium deficiency have disappeared.

2. *Method of Administration:* Most of the mixtures that have been described are best given intravenously by continuous drip infusion. In babies a scalp vein can be used, the head being immobilized by sand bags and the arms and body by blankets or other restraints,[6] or a small

canula may be fastened into an exposed ankle vein.[13] The subcutaneous route may be used when necessary for any of the saline mixtures, but fluids given in this way should not contain any more than 2.5 per cent glucose.[6] In conscious cooperative adults the small veins of the hand or forearm near the wrist should be used, with the intravenous needle securely fastened into place by adhesive strapping so that the patient is able to bend his elbow freely and without restraint. In the unconscious or uncooperative patient it will be necessary to secure the limb into which the fluid is being given in such a way that the needle is held firmly and cannot be dislodged no matter how vigorously the patient may thrash about or try to remove it. It is best, once the intravenous has been successfully started, to continue it, if possible, without stopping until it is no longer required. Chute[9] recommends that difficulties in administration, associated with clotting and thrombosis within the vein being used, be avoided by the addition of an amount of heparin just sufficient to give in the final mixture a concentration of 1 unit per cc. (0.1 cc. Connaught Laboratory heparin solution, containing 1000 units per cc., in each 100 cc. intravenous fluid).

3. *Rate of Administration:* The rate of administration of intravenous fluids to severely dehydrated patients should be fairly rapid during the initial stages of treatment. In babies as much as 15 cc. per lb. (33 cc. per Kg.) may be run in quickly within the first fifteen minutes[46] and a further 15-30 cc. per lb. may be given during the course of the next twelve hours by slow intravenous drip. Adults may receive their fluids at an initial rate of 500-1000 cc. per hour until 1500-2000 cc. or more have been given. Slower rates are used in older people and in those who have evidence of cardiovascular disease, and in all cases the patients are watched carefully for any signs of pulmonary or other congestion. Once the dehydration has been relieved, the speed of the flow should be slowed and the number of drops per minute (20 drops are approximately 1 cc.) so adjusted that the desired daily maintenance dose is evenly spread out over the 24 hours. It is also desirable, except in patients who are losing salt, to replace the normal saline with a mixture of two-thirds 5 or 10 per cent glucose and one-third normal saline after the salt depletion has been corrected.

4. *Amount of Fluid and Electrolyte to be Given:* It is not possible to determine beforehand by any laboratory test or blood examination just how much water and salt or other electrolyte should be administered. The approximate needs of a given patient are best determined by his clinical condition at the beginning, and the ultimate amount administered should be governed by his response to treatment. Careful clinical notes by the attendant nurses, giving attention particularly to the mental state of the patient, the pulse rate, respirations, blood pressure, and urinary

output, and frequent examinations by the physician in charge will enable the effect of therapy to be accurately assessed and will indicate in what way it should be altered or changed. The objectives are to give enough fluid and salt to abolish the water and sodium chloride depletion, to restore, if it is disturbed, the acid-base balance to normal, and to compensate for all the inevitable and abnormal losses. This may require in a 70 Kg. adult as little as 1.5 L. or as much as 6–10 L. of the appropriate kind of fluid. Good evidence that these aims have been successfully accomplished will be furnished by the improvement in the patient's clinical condition and by the excretion, during each eight-hour period, of 500 cc. or more urine containing appreciable amounts of salt (3-5 Gm. per L.).[33]

In many cases of acidosis there will be no need to give any electrolyte other than physiologic saline, but in others it may be desirable to administer sodium bicarbonate or sodium lactate as well. Attempts have been made in these cases to calculate from the patient's weight and the plasma bicarbonate of his plasma how much alkali should be given but these have not met with any great success and are hardly worth while.[7] Here again it is best to regulate the amount required by the clinical evidence of acidosis, helped if desired by serial determinations of the plasma bicarbonate level. Normal saline will also often be effective in the treatment of shock which is *not* due to hemorrhage or plasma loss. In some cases, however, it may be desirable to supplement the intravenous fluid with a transfusion, giving 10-30 cc. whole blood or plasma per Kg. of body weight; and such amounts and more if necessary of these should always be given when shock has been caused by hemorrhage or by loss of plasma.

BIBLIOGRAPHY

1. Asper, S. P., Schales, O., and Schales, S. S. Importance of controlling *p*H in the Schales and Schales method of chloride determination. *J. Biol. Chem.* 168:779, 1947.
2. Benedict, F. G. A study of prolonged fasting. Pub. 203, Carnegie Institute of Washington, 1915.
3. Black, D. A. K., McCance, R. A., and Young, W. F. A study of dehydration by means of balance experiments. *J. Physiol.* 102:406, 1944.
4. Blalock, A. Principles of Surgical Care; Shock and Other Problems. St. Louis, Mosby, 1940.
5. Brown, M. R., Currens, J. H., and Marchand, J. F. Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis. *J.A.M.A.* 124:545, 1944.
6. Butler, A. M., and Talbot, N. B. Parenteral fluid therapy. I. Estimation and provision of daily maintenance requirements. *New England J. Med.* 231:585, 1944.

7. Butler, A. M., and Talbot, N. B. Parenteral fluid therapy. II. The estimation of losses incident to starvation and dehydration with acidosis or alkalosis and the provision of repair therapy. *New England J. Med.* 231:621, 1944.
8. Bulmer, F. M. R. Use of added salt in industry in Ontario. Personal communication, 1948.
9. Chute, A. L. Personal communication, 1948.
10. Darrow, D. C. Body fluid physiology: The relation of tissue composition to problems of water and electrolyte balance. *New England J. Med.* 233:91, 1945.
11. Darrow, D. C. The retention of electrolyte during recovery from severe dehydration due to diarrhoea. *J. Pediat.* 28:515, 1946.
12. Darrow, D. C. Disturbances in electrolyte metabolism in man and their management. *Bull. New York Acad. Med.* 24:147, 1948.
13. Drake, T. G. H. Personal communication, 1948.
14. Elkinton, J. R., and Winkler, A. W. Transfers of intracellular potassium in experimental dehydration. *J. Clin. Investigation* 23:93, 1944.
15. Fantus, B. Fluids postoperatively: A statistical study. *J.A.M.A.* 107:14, 1936.
16. Fenn, W. O. The role of potassium in physiological processes. *Physiol. Rev.* 20:377, 1940.
17. Finch, C. A., Sawyer, C. G., and Flynn, J. M. Clinical syndrome of potassium intoxication. *Am. J. Med.* 1:337, 1946.
18. Frenkel, M., Groen, J., and Willebrands, A. F. Low serum potassium level during recovery from diabetic coma: With special reference to cardiovascular manifestations. *Arch. Int. Med.* 80:728, 1947.
19. Gamble, J. L. Extracellular fluid: Extracellular fluid and its vicissitudes. *Bull. Johns Hopkins Hosp.* 61:151, 1937.
20. Gamble, J. L. Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid. Cambridge, Harvard, 1947.
21. Gamble, J. L., Ross, G. S., and Tisdall, F. F. The metabolism of fixed base during fasting. *J. Biol. Chem.* 57:633, 1923.
22. Govan, C. D., and Darrow, D. C. The use of potassium chloride in the treatment of the dehydration of diarrhoea in infants. *J. Pediat.* 28:541, 1946.
23. Hartmann, A. F., and Elman, R. E. The effects of loss of gastric and pancreatic secretions and methods for restoration of normal conditions in the body. *J. Exper. Med.* 50:387, 1929.
24. Holler, J. W. Potassium deficiency occurring during the treatment of diabetic acidosis. *J.A.M.A.* 131:1186, 1946.
25. Kerpel-Fronius, E. Über die Beziehungen zwischen Salz-und Wasserhaushalt bei experimentellen Wasserverlusten. *Ztschr. fur Kinderh.* 57:489, 1935.
26. Ladell, W. S. S., Waterlow, J. C., and Hudson, M. F. Desert climate: Physiological and clinical observations. *Lancet* 2:491 and 527, 1944.

27. LASHMET, F. H., and NEWBURGH, L. H. A comparative study of the excretion of water and solids by normal and abnormal kidneys. *J. Clin. Investigation* 11:1003, 1932.

28. MCCANCE, R. A. Experimental sodium deficiency in man. *Proc. Roy. Soc. London, s. B* 119:245, 1936.

29. MCCANCE, R. A. Medical problems in mineral metabolism. *Lancet* 1:643, 704, 765, and 823, 1936.

30. MCCANCE, R. A. The effect of salt deficiency in man on the volume of the extracellular fluids and on the composition of sweat, saliva, gastric juice and cerebrospinal fluid. *J. Physiol.* 92:208, 1938.

31. MCCANCE, R. A., and YOUNG, W. F. The secretion of urine by new born infants. *J. Physiol.* 99:265, 1940–1941.

32. MCCANCE, R. A., and YOUNG, W. F. Observations on water metabolism. *Brit. M. Bull.* 2:219, 1944.

33. MARRIOTT, H. L. Water and salt depletion. *Brit. M. J.* 1:245, 285, and 328, 1947.

34. MARTIN, H. E., and WERTMAN, M. Serum potassium, magnesium, and calcium levels in diabetic acidosis. *J. Clin. Investigation* 26:217, 1947.

35. MOSS, K. N. Some effects of high air temperatures and muscular exertion upon colliers. *Proc. Roy. Soc. London, s. B* 95:181, 1923.

36. NADAL, J. W., PEDERSEN, S., and MADDOCK, W. G. A comparison between dehydration from salt loss and water deprivation. *J. Clin. Investigation* 20:691, 1941.

37. NICHOLSON, W. M., and BRANNING, W. S. Potassium deficiency in diabetic acidosis. *J.A.M.A.* 134:1292, 1947.

38. PETERS, J. P. Body Water: The Exchange of Fluids in Man. Springfield, Ill., C. C. Thomas, 1935.

39. PETERS, J. P. Water Balance in Health and Disease, in DUNCAN, G. G.: *Diseases of Metabolism.* Philadelphia, W. B. Saunders Co., 1947.

40. SCHALES, O. and SCHALES, S. S. A simple and accurate method for determination of chlorides in biological fluids. *J. Biol. Chem.* 140:879, 1941.

41. SHERMAN, H. C. Chemistry of Food and Nutrition (ed. 7). New York, Macmillan, 1947.

42. SHOHL, A. T. Mineral Metabolism. New York, Reinhold, 1939.

43. STENNING, J. C. Salt deficiency states in tropical climates. *J. Roy. Nav. M. Serv.* 31:129, 1945.

44. Subcommittee on Shock and Blood Substitutes of the Associate Committee on Medical Research, National Research Council of Canada. The early recognition and treatment of shock. *Canad. M. A. J.* 48:196, 1943.

45. THORN, G. W., DORRANCE, S. S., and DAY, E. Addison's disease: Evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients. *Ann. Int. Med.* 16:1053, 1942.

46. TISDALL, F. F., and DRAKE, T. G. H. Personal communication, 1948.

Chapter 13

IODINE MALNUTRITION[*]

George M. Curtis and M. Been Fertman

The role assigned to iodine in the pathogenesis of thyroid disease has not been a contrivance of the modern mind. Though unacquainted with that element, the ancients had become familiar, through either shrewd deduction or fortunate empiricism, with the use of burnt sponge and seaweed in the treatment of goiter. It was not until this time-tested lore had been submerged in the ignorance of the Dark Ages, the Renaissance had flourished and declined, and the modern industrial epoch had been ushered in, that the unknown magic in seaweed was unveiled as the element iodine. This important revelation, as so many others, came to mankind through incidental circumstance. Courtois in 1811, perplexed as to why his copper vats, containing a lye made from seaweed used in preparing Napoleonic war materials, were corroding, sought and found his answer in seaweed-liberated iodine. Thus, like atomic fission, the discovery of iodine resulted from the stimulus of military necessity.

Close upon the discovery of iodine followed its isolation by Sir Humphrey Davy from sponges and other forms of marine life. Two enterprising Swiss physicians, Coindet (of Geneva) and Straub (of Bern), quick to sum up the accumulated wisdom and transform it into service, employed iodine as early as 1820 in the treatment of goiter. There followed a fruitful century of clinical investigation extending to Plummer of

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Rochester, and fundamental experimental researches dating from Boussingault of Paris on through Chatin, Baumann, Kendall, Marine, von Fellenberg, and others to Harington of London.

Today iodine prophylaxis against the development of goiter is widely recognized, while iodized salt is used throughout the entire United States.[80] The extensive and increasing popularity of iodized salt obtained an original impetus from the experiments of Marine and Kimball in Akron, Ohio. It gained momentum through the success of the Swiss with iodides in their long attempts to control goiter and its tragic sequel, endemic cretinism.

As has so often happened in the sweep of medical progress, the treatment and even the mode of prevention of a given disease may be in vogue long before the true rationale becomes clear. So it was with iodine in thyroid disease.

In 1896 Baumann isolated iodine from the thyroid gland and demonstrated it to his colleagues in its characteristic violet vapor form.[2] Baumann, Oswald, and others thought that the active principle formed by the thyroid was thyreoglobulin and, in general, that the thyroid iodine content varies directly with the amount of stainable colloid and inversely with the degree of glandular hyperplasia. Attempts to clarify this relationship between physiologic activity and the presence of iodine, however, led only to controversies until Kendall in 1914 isolated in crystalline form a substance which he called *thyroxine*, containing iodine and possessing physiologic properties of the dried whole thyroid gland.[46]

Isolation of the thyroid hormone was repeated by Harington,[39] who, with sufficient quantities available, determined the correct molecular structure. Working from this structural formula, he succeeded in synthesizing thyroxine. Thyroxine is 65 per cent iodine. The administration of this iodine-rich hormone to animals or to man was found to produce a rapid increase in pulse rate and vigor as well as an increase in metabolism and nervous irritability.

PHYSIOLOGY

Weighing ordinarily about 25 Gm. and containing around 10 mg. iodine, the human thyroid gland normally maintains an iodine concentration of around 40 mg. per 100 grams. When this concentration falls below 10 mg., hyperplasia ordinarily ensues and goiter may develop.[64]

No other organ of the body has the power of iodine concentration possessed by the thyroid gland. The whole-blood iodine averages less than 1 part in 25 million, while the thyroid gland normally contains approximately 1 part in 25 hundred. This indicates that the thyroid gland can concentrate the iodine it obtains from the blood by a factor of at least 10,000.

Within the colloid in the alveoli of the thyroid gland, iodine is largely stored in the form of the amino acids diiodotyrosine and thyroxine, containing respectively 59 and 65 per cent iodine. The demonstrated facts of thyroid physiology indicate that iodine is selectively absorbed by the active thyroid gland. Furthermore, in some measure the glandular function is regulated by its iodine content. Studies with radioactive iodine have shown that ingested iodine is quickly brought to the gland by the blood stream and rapidly converted by the thyroid gland into complex organic compounds. Within a few hours these organic iodine compounds, just manufactured by the cellular activity of the follicle wall,[51] may return to the circulation.[73]

A basic tendency of this regulating gland, first observed before the turn of the century,[2] is toward an increase in weight when its iodine content is low and conversely a diminution when its iodine concentration is high. Moreover, the thyroid iodine is low with either a high incidence of nodule formation or a high percentage of epithelial proliferation.[49] It is low with increased height of the follicular epithelium, with lymphocytic infiltration, and with the occurrence of degenerative changes in the gland. In diffuse colloid goiter the concentration of iodine is definitely below that found in the normal gland.[49]

When normal or goitrous thyroid glands, obtained from goitrous regions, are compared with glands of similar status from other regions, it is found that those from the goitrous regions are the larger and have the higher incidence of nodule formation, the smaller follicular size, and the lower iodine content.[49]

The iodine which the individual consumes in his daily food, *and absorbs,* is the principal factor in determining the iodine content of the thyroid gland, its net effect overshadowing any differences which may be due to species, age, or sex. Even small differences in the iodine intake are reflected in the iodine content of the gland.[72] If iodine is withheld, compensatory hypertrophy and even hyperplasia of the thyroid occurs.[51] The addition of sufficient iodide to the diet, however, will prevent the subsequent development of goiter.[79]

Since iodine intake is so largely dependent on the amount of iodine in the soil and its vegetation, the gland concentration varies with the geographic distribution of iodine.[32] There are seasonal variations in the amount of iodine found in the thyroid,[47, 49] but these may be attributed to seasonal variation in the amount of iodine in the available foodstuffs.[65, 72]

IODINE LEVELS

The amount of iodine in the blood stream has for many years merited special consideration. It is an index of thyroid function and of the metabolism of iodine. When fractionated it is a rough measure of the release of thyroid hormone and of its breakdown within the body. With radioactive tracer methods this measure has become more exact. With improving technics in the fractionation of the blood iodine, there is emerging a means of distinguishing the circulating thyroid hormone from its breakdown products in the blood stream. Meanwhile, studies of the whole-blood iodine, and particularly of the protein-bound fraction, serve, along with basal metabolic rate determinations, in differentiating the various thyroid diseases from each other, and in distinguishing them from normal and from nonthyroid clinical conditions.[19, 20]

Human blood normally maintains a fairly constant level of iodine. Fractionation studies reveal that about one-fourth of this *presumably* represents the circulating thyroid hormone.[22] The other three-fourths, consequently, would represent the iodine of nutrition together with products of the breakdown of the iodine-rich hormone.

Various values, ranging from 3 to 20 micrograms per 100 cc., have been ascribed by different investigators to the normal blood iodine level.[21] These vary with the method of iodine determination and the geographic area, as well as with certain physiologic factors. The blood iodine is significantly increased in pregnancy, in parturition, in toxic nodular and in exophthalmic goiter: as well as in certain nonthyroid disorders.[10-12, 14] It is increased when iodine in any form is administered.[9, 29, 78]

In hypothyroidism the whole-blood iodine is often within normal limits.[11, 12] Nevertheless, the acetone-insoluble fraction, which presumably contains the circulating thyroid hormone, is diminished to an average of about one-half normal.[22] In nontoxic nodular goiter this fraction will show an average increase over normal,[19] even when the whole-blood iodine does not.[11, 12]

The blood iodine does not always increase or decrease along with the basal metabolic rate.[11, 12, 14] The latter is a less exclusively controlled function of the thyroid gland than the circulating iodine and is, in fact, the resultant of several different bodily processes. However, there is a significant correlation between the blood iodine and the basal metabolic rate in thyroid disease, noted particularly in those goitrous conditions attended by hyperthyroidism,[11, 12, 20] as well as in nontoxic nodular goiter.[11, 12, 19, 20] A study of this relation unmasks the subtle development of hyperthyroidism in previously quiescent nodular goiters.[19, 20]

The urinary iodine is another measure of the metabolism of iodine. Under maintained basal hospital conditions, together with a monotonous diet, the normal adult excretes a surprisingly constant amount of iodine in the urine.[18] The urinary iodine varies directly with the geographic iodine supply and inversely with the incidence of goiter.[18, 29]

Several factors tend to increase the amount of iodine lost in the urine. These include hyperthyroidism,[15] menstruation,[8] pregnancy,[30] surgery,[16] and the administration of iodine in all forms studied.[16-18] On the other hand, fasting decreases the urinary excretion of iodine.[17]

Iodine is also present in other body fluids. It has been demonstrated in the lymph, cerebrospinal fluid, perspiration, chyle, ascitic fluid, pleural exudates, and in milk. In milk it plays the important role of supplying the needed iodine to the growing infant, even at the expense of the mother's iodine stores.[70]

GEOGRAPHIC DISTRIBUTION AND ENDEMIC GOITER

The singular association of the geographic distribution of iodine with the prevalence of endemic goiter has been convincingly demonstrated. There is, however, left to the imagination concerning other cause-and-effect relationships, the goitrogenic substances found in certain foods.[78, 85] Where there is notable deficiency of iodine in the soil and consequently in the water and foodstuffs, goiter and even cretinism become endemic. Thus, the highest incidence of goiter has been found among the Alps, Pyrenees, and Himalayas; in the Thames Valley in England, in certain inhabited districts of New Zealand, in the region of our own Great Lakes, and in the Pacific Northwest.[55]

The Swiss have had to contend with this problem in its gravest form, endemic goiter with closely associated endemic cretinism, and have found a workable solution in iodine prophylaxis. More recently a similarly acute situation was noted in the Far East, in the Chinese province of Yunnan.[81] Because of military occupation by the Japanese, the hinterland of China had been cut off from its former coastal supply of salt. Large sections of China were thus forced to depend on Yunnan salt. The appearance of goiter and cretinism in Yunnan alone was considerable. Men and women workers on the Burma Road were showing an incidence of thyroid enlargement often as high as 80 per cent. Mere residence in a Yunnan goitrous district for as little as six months would condemn susceptible individuals to the development of thyroid disease.[81]

The goiter problem, hand in hand with diminished iodine intake, also lies close at home. Throughout the United States there are varying degrees of iodine deficiency, dependent on the local geologic conditions of the soils and waterways. A high incidence of goiter is especially noteworthy in the Central Plain of North America, where regional iodine is low.[55] On the sea coasts, where large amounts of iodine-rich sea foods are consumed, there is a minimum of endemic goiter. Moreover, division of the country into sections according to the iodine content of its waters reveals that the incidence of goiter is high where the iodine in the water is low.[33, 55] Such regions are included in a section extending from Oregon to the western part of Maine and from Nevada to the western part of Virginia.[55]

Endemic goiter is closely related to the iodine intake in any given region; more specifically, it is directly related to the proportion of the intake which is ultimately metabolized. About 14 micrograms* daily was formerly stated to represent the difference in iodine intake between goitrous and nongoitrous regions.[31, 40] However, these regional differences in iodine consumption have become less pronounced as the interstate transportation of food, drinks, vegetables, fruits, and fertilizers has increased.

The dietary habits of its people may decide the goiter incidence of any nation. This is strikingly illustrated by the contrasting situations prevailing in Japan and Formosa, both geologically low in iodine.[55] The incidence of goiter is high among the Formosan population but is almost unknown among the Japanese, whose great appetite for seaweed leads them to import large amounts of this iodine-rich foodstuff for mass consumption.

The iodine concentration of one important foodstuff, milk, is generally reliable as an index of the extent of goiter prevalent in that region.[72, 86] This is because the amount of iodine secreted in the milk ultimately depends, barring all iodine supplements, on the quantity of this element in the herds' diet.[70, 86]

ABSOLUTE AND RELATIVE IODINE DEFICIENCY

In those regions geographically low in iodine, where the intake of iodine is consequently inadequate, there is found among humans endemic goiter and sometimes cretinism; among the domestic animals there occurs thyroid enlargement, together with breeding difficulties and *fetal athyrosis*. Beside these more obvious anomalies there are many borderline conditions induced by varying deficits in the iodine intake.

The ultimate cause of endemic goiter and its sequelae is not clear. The immediate cause is a deficiency of iodine, an element essential in the production of the iodine-rich thyroid hormone. This iodine deficiency may be absolute, as in areas where the iodine intake is subnormal; or relative, depending upon the various demands of the body[29] as well as upon the interplay of multiple factors which determine the availability of ingested iodine for metabolic use in the organism. Conditions increasing the need of thyroid secretion, and thus the organic requirement of iodine, include the stress and change involved in puberty, in pregnancy, and in lactation. Infectious processes and poor sanitation may act similarly.[54]

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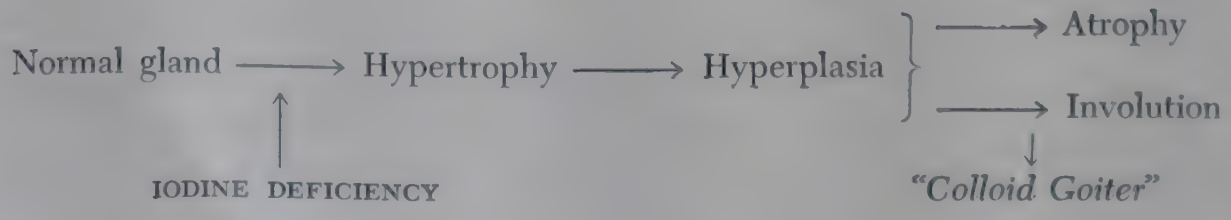
* A microgram is one thousandth of a milligram, or 0.000001 Gm. An ounce has about twenty-eight grams.

Other factors which either reduce the efficiency of the iodine supply or increase the demand are certain dietary components[54] as well as certain toxic substances.[85] Thus, a high calcium diet results in a greater and more rapid increase in the size of the thyroid glands of animals maintained on a low iodine intake.[6] Deficiency in the supply of vitamin A may also induce goiter when the iodine intake is in the lower normal range.[54] This becomes of further significance in the light of more recent studies showing that vitamin A deficiency apparently increases the rate of formation of thyroxine.[53] Moreover, vitamin A, when given in massive doses to patients with hyperthyroidism, results in a rapid decrease of the basal metabolic rate, an increase in the level of the blood cholesterol, and an improvement in the symptoms.[88]

Cabbage, Brussels sprouts, soy beans, ground nuts and other foodstuffs[78, 85] can, apparently as a consequence of an extractable goitrogenic substance,[85] induce goiter in rabbits. Other factors interfering with the gastrointestinal absorption of iodine may also lead to metabolic iodine deficiency. Pork and excess fats are more than suspect in this regard.

COLLOID GOITER AND CRETINISM

The enlarged thyroid in endemic goiter reveals a variety of histologic forms. In the early stages, diffuse enlargement occurs, with colloid distention of the follicles, resulting in the usual "colloid goiter." Despite its abnormal histologic appearance, the hyperplastic gland usually maintains its normal physiologic function. However, it may eventually approach exhaustion atrophy, in which case the alveoli become distorted and compressed, with the follicular epithelium high and irregularly arranged. These alterations may be explained on the basis of the following cyclic changes:



Experimentally, at least, hyperplasia can be readily induced as a compensatory reaction to the lack of iodine.[60, 61, 79] A deficient iodine supply or an increased need for thyroid hormone serves as a stimulus to hypertrophy,[61] and with further continued stimulation, hyperplasia ensues. Eventually, this may even lead to atrophy. If, however, the stimulation ceases, involution sets in and the accumulation of iodine-poor colloid in the involuted gland gives rise to a "colloid goiter." This process may repeat itself with a renewal of the cycle.

In long-standing goiter, thus predisposed to pressure atrophy, vascular degenerative changes, edema, hemorrhage with necrosis and cystic degeneration, there is a tendency for the cyclic process to become more localized and for the gland to become nodular in character. Further developments may then follow, even with the onset of neoplastic change. The development of carcinoma occurs more frequently in nodular goiters than in normal thyroid glands.[68]

The simple goiter is often capable of elaborating an adequate amount of thyroid hormone, and consequently the characteristic symptoms of an associated hypothyroidism are not always encountered. The simple goiter manifests itself chiefly in a mechanical manner. In addition to gross disfigurement, there may ensue, as a consequence of compression of the trachea and other cervical structures: stridor, chronic nonproductive cough, dysphagia, congestion of the face, hoarseness, and even Horner's syndrome.

The basal metabolic rate[4, 11, 12] as well as the whole-blood iodine[11, 12] are within normal bounds in simple colloid goiter. There is a tendency toward hypothyroidism. In the subsequently developing nodular goiter, the average basal metabolic rate may be significantly increased even when clinical hyperthyroidism has not as yet become manifest.[11, 12] An increase is also noted in the protein-bound blood iodine[19] but may not be detected in the whole-blood iodine.[11, 12]

The diagnosis of *colloid goiter* depends upon the appearance and "feel" of the diffusely and evenly enlarged gland, as well as upon the absence of the signs and symptoms of hyperthyroidism. A careful analysis of the pulse rate during rest, together with the negative laboratory findings (basal metabolic rate, protein-bound blood iodine, and serum cholesterol) are additional aids in making the differential diagnosis. Other factors which should be kept in mind are the geographic occurrence of simple colloid goiter, its tendency to develop at or before puberty, and its preponderance among schoolgirls.

A hundred years ago Dr. Hugh Norris[69, 71] reported a high incidence of cretinism in Somersetshire. So goitrous was this district that the "offspring of strangers acquire bronchocele* if they become residents in the place at an early age." In this little village goiter was frequent among the noncretinous residents as well. Consequently Norris concluded that cretinism is not only accompanied, but also in some measure is caused by the presence of goiter.

In regions where goiter is endemic, and more rarely elsewhere, cretinism may be found. Its incidence is directly proportional to the severity and duration of the endemism. The two diseases are thus closely related. "Goiter is the earlier effect of the endemic influence; cretinism shows itself when the action of that influence is intensified by operating on more than one generation," was the observation of Flagge as early as 1871.[34]

Iodine lack in the first generation or two will result in the development of simple colloid goiter. In the offspring of mothers made goitrous by severe iodine deficiency, cretinism appears as a consequence of an inadequate supply of iodine to the thyroid gland of the developing fetus. Among animals[63] and man as well (the Swiss for example) goitrous mothers ordinarily giving birth to cretins will produce normal offspring if fed sufficient iodine during the period of pregnancy.

Like colloid goiter, cretinism is usually endemic and but rarely sporadic. The endemic cretin sometimes presents a goiter which may be of huge size, at other times a barely palpable atrophic thyroid. The sporadic cretin always presents an atrophic, if not an almost congenitally absent, thyroid. Retardation is generally less marked in those endemic cretins who have the apparent good fortune to develop goiters.[43, 69]

Cretinism is characterized by dwarfism, together with varying degrees of mental retardation. Insufficient development of both the white and grey matter, stemming from a marked inadequacy of thyroid hormone at an early stage, reveals itself in an apathy, defective speech, clumsy gait, incontinence, and other maldevelopments of the neuromuscular system. As a result of inhibited skeletal growth, the cretin, as he ages, preserves the bodily proportions of the newborn infant. His appearance is characteristic, with coarse, "pig-like" facies, for the most part expressionless, tongue thick and protruding, pot-belly, and puffy pads on the buttocks and back of the shoulders.[69, 87] The basal metabolic rate is reduced from −20 per cent to −40 per cent. Among the many signs and symptoms, there are found a rough and scaly skin, wide and flaring nostrils, sparse or falling hair, thin and brittle nails, spadelike hands and feet, and thick lips. In addition, there may be anorexia, constipation, delayed and imperfect dentition, and a characteristic pallor, often with an associated anemia.

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* The older term for goiter.

A form of late-developing cretinism, or *juvenile myxedema,* is occasionally encountered. Here the clinical picture is modified by the extent of normal growth and differentiation which has preceded the onset. The role of iodine deficiency, so well demonstrated in endemic cretinism and in endemic goiter, is less certain in the juvenile or in the adult types of acquired hypothyroidism. It would seem, however, that under certain abnormal conditions, insufficient iodine for the synthesis of adequate thyroid hormone, particularly in the absence of a compensatory hyperplasia of the thyroid gland, might induce one of the late manifestations of endemic cretinism.

GRAVES' DISEASE

The mechanism which causes a goiter to become "toxic" is at present obscure. The ensuing hyperthyroidism is apparently the result of a variety of interacting factors. The role of iodine malnutrition in the etiology of "toxic" goiter remains controversial. Although it has never been convincingly demonstrated as a cause, it may be at least remotely related, for example, by a train of events from "simple colloid goiter" to goiter with nodule formation, and from a "nontoxic nodular" to a "toxic nodular goiter." If so, then certain forms of "toxic" goiter may be prevented by an adequate iodine intake.

Marine, from his study on animals, concluded[57] that Graves' disease in man might be a step toward the development of myxedema. ". . . I am also inclined to think that the more we study toxic (exophthalmic) goitre, the more closely we shall find it related to the cretinoid conditions of dog, sheep and cattle; also that it is a reaction to a deficiency, and if the deficiency is met the gland reverts to a colloid type, and if not, the organism exhausts itself in the attempt to meet the deficiency." Marine's view was thus in contradistinction to the hypersecretion theory of Moebius and Gauthier.

Plummer demonstrated that after the administration of large doses of iodine to patients with Graves' disease there occurs a remarkable and sudden decline in the symptoms and a characteristic fall in the basal metabolic rate.[75] Consequently he advanced the hypothesis that an insufficiently iodinated thyroid hormone is produced in exophthalmic goiter. This unsaturated thyroid hormone was thought to be more capable of entering into certain catalytic metabolic activities. However, when mono-, di-, and tri-iodothyroxine are given experimentally the metabolic response is less than that when thyroxine is given.[36] The increases in the protein-bound blood iodine in exophthalmic goiter are also difficult to explain if one accepts the theory that an unsaturated thyroid hormone is formed. It is more likely that iodine-induced remissions are produced by the inactivation of thyrotropin by iodine[1] or to the inactivation of those enzyme systems governing the release of thyroid hormone from thyroid follicles.[26, 27, 77] Nevertheless, by developing the principle of preoperative iodinization Plummer and his surgical associates, and later the surgical world, were able greatly to diminish the postoperative deaths from hyperthyroidism.

Since Plummer's significant contribution iodine has been used extensively for this purpose and with continued good results. In milder cases, iodine medication alone, and more recently antithyroidal agents, may cause the thyrotoxicosis to subside. Permanence of the effect of iodine in causing an abatement of the symptoms is still a matter of controversy.

Improvement in symptoms following iodine therapy is reflected in the histologic appearance of the gland: an increase in colloid store, decreased vascularity, and involution of the hyperplastic epithelium. The exact mechanism by which this occurs, however, is not clear. There is as yet no comprehensive explanation for the decrease in circulating hormone in the blood, storage of iodine and hormone in the gland, and the formation and retention of colloid in the follicles, following iodine therapy. The amount of iodine necessary to elicit an optimal response in Graves' disease is much greater than that involved in the normal iodine metabolism of the body.

OTHER IODINE-DEFICIENCY DISEASES

There are various other pathologic conditions which, because of their response to iodine treatment or prophylaxis, appear to be wholly or in part manifestations of iodine malnutrition. Some may be in a way associated with changes in the usual thyroid function.

It should first be clearly understood that iodine is present in organs other than the thyroid gland.[44, 49, 52] It is also found in varying concentration in the extrathyroid body tissues and in the various body fluids. The role it plays in these tissues and in the body fluids is not clearly understood.

Because of the close relationship which each other endocrine gland bears to the thyroid, their iodine content becomes of practical significance. Certain studies indicate that they exceed the nonendocrine tissues in iodine concentration.[67, 89] Others do not.[49, 52] Moreover, the "master gland," the pituitary, whose reciprocal relations with the thyroid are so well appreciated, has a low iodine content.[49, 52] This is similarly true of the central nervous system itself.

Considerable importance has been attached to the role of the liver in the physiology of iodine.[29] Nevertheless, its actual position in this regard remains an enigma. The conviction that this vital organ, which enters into so many of the body's indispensable activities, also exerts an influence on iodine metabolism, arises from various experimental and clinical findings. Thus, elevation of the whole-blood iodine, often marked, has been observed in patients with a damaged liver or with diseases of the biliary tract.[23-25] Moreover, the iodine content of normal bile is consistently high.[49, 52] Bile is next to hair and then to the thyroid gland in iodine concentration in the human body.[52] Perhaps in some way these phenomena are related to the "antithyrotoxic" substance recently isolated from the liver.[3]

Evidence that iodine malnutrition may play a role in gonad-thyroid relationship seems to be forthcoming from data on lactation and on breeding problems involving sterility and stillbirths. Its effects in causing breeding difficulties in particular are well known. Breeding difficulties among domestic animals existed in varying degrees throughout the goiter areas of the United States,[45, 57, 90] until the prophylactic use of iodine became widespread as a means of combating this problem.

As early as 1907 iodine-containing salts were fed to Michigan sheep in order to prevent the high death rate ordinarily occurring among the newborn.[57] In 1916 Montana, faced with a high mortality among its livestock, as well as with the development of goiter and underfunctioning thyroid glands, instituted similar therapy with considerable success.[90] Since the introduction of iodized salt in 1920 at the University of Wisconsin Farms, there has not been an instance of goiter among the domestic animals, including sheep, swine, colts, and calves.[80]

Iodine prophylaxis of iodine-deficiency disease among animals, or *fetal athyrosis* as it was designated, has spread to various other states and provinces, including Minnesota, the Dakotas, Wyoming, Washington, Idaho, southern Alberta, and British Columbia.

When supplemental iodine is given to cows, not only is there increased fertility, along with a reduction in the number of stillbirths and goitrous calves, but also milk production is significantly augmented.[74] Improved lactation has been noted among women taking iodine.[82] A preliminary report on the effect of iodine on failing lactation suggests that this is due, not to a defective thyroid gland, but to a deficient iodine intake. All mothers treated with iodine were found to respond with an increase in the output of breast milk.[82]

Iodine malnutrition appears to play a significant role in the general health, growth, and development of man and his domestic animals. This may very well be due to its high concentration (65 per cent) in the potent thyroid hormone. Moreover, the thyroid hormone interacts with the secretions of the other endocrine glands.

In an extensive study of Swiss school children during 1920 and 1921, Hunziker[41, 42] showed that 339 boys from 6 to 16 years of age who received iodine grew an average of 7 mm. more than 223 untreated boys of the same age range, and put on 200 Gm. more in weight. The mean weight at birth of infants whose mothers were receiving iodized salt was 100 Gm. greater than that of control infants.[72] Among Swiss recruits a significant increase in average height was noted during an era of iodine administration (1908–1912).[41] Moreover, the average height of recruits varied inversely with the incidence of goiter prevailing in the sections from which they came.

Feeding milk with an increased iodine content to children living in a region of high goiter incidence resulted in more rapid and regular growth and development.[91] Administration of optimal amounts of iodine to nursing animals accelerated the rate of growth and weight of their young.[66, 72] Direct iodine administration to the young was likewise beneficial.[38]

THERAPY

In iodine malnutrition, prevention and treatment are most intimately connected. Yet, of the two, prophylaxis, when readily attainable, *is of the greater significance* and is more far-reaching and consequently more gratifying in its effects. In areas of endemic cretinism treatment of the goitrous inhabitants becomes prophylaxis to the potentially cretinous succeeding generations.

The first objective large-scale experiments, convincing as to the value of an adequate iodine intake, were conducted in an area presenting considerable endemic goiter but little cretinism. David Marine,[62] after demonstrating the significance of iodine deficiency in animals, turned to the investigation of human thyroid disease. Almost 7000 Ohio school girls were followed for a period of from one to two and one-half years. Those who showed no thyroid enlargement initially, as well as the one-third who did, were voluntarily divided into almost equal groups. One became a control group, the other received 200 mg. of sodium iodide daily over a period of two weeks, each spring and each fall. Among those who showed no goiter originally, only 0.2 per cent receiving iodine, as compared with 21.5 per cent of those who did not, developed enlarged thyroid glands. Among the girls with initial thyroid enlargement, 65.4 per cent of those receiving iodine showed a reduction in the size of their glands, in contrast to only 13.8 per cent of the untreated girls in this group.[62] From this same study Marine and Kimball concluded that goiter is most likely to develop during fetal life, puberty, or pregnancy.

The character and results of the Ohio demonstration stimulated other similar efforts throughout the world, particularly in Switzerland, Austria, and Germany. Iodine prophylaxis in Switzerland brought with it a steady decline of cretinism, such an important economic factor to the Swiss. Until 1922 every other infant in the canton of Appenzell began life with an enlarged thyroid gland. The institution of iodized salt in that year led to the virtual disappearance of goiter in the newborn. The use of iodized salt in the canton of Vaud, likewise a result of the efforts of the Swiss Goiter Commission, brought about a decline in the incidence of goiter from 77 to 21 per cent in approximately fifteen years.[28]

Promotion of the use of iodized salt in Michigan in 1924 led, over a period of eleven years, to declines of from 75 to 90 per cent in the incidence of goiter in different counties.[33] The incidence of goiter operations in seven large hospitals in southern Michigan dropped from 1452 in 1927 to 591, considerably less than one-half, in 1933. There was a 60 per cent decrease in goiter operations as compared with a 17 per cent all-operation decrease during the corresponding depression years.[56]

The convincing results in Michigan were attained by using a salt containing 0.02 per cent sodium iodide. More recently the National Study Committee on Endemic Goiter concluded that a sufficient quantity, after a stabilizer was added, is 0.01 per cent of potassium iodide. Calculated on the basis of an average daily consumption of 6.2 grams of salt, this would furnish 474 micrograms of iodine daily.[33, 80] The daily intake of iodine derived in this manner[13] would be more than twice the optimal amount necessary, as obtained from a consideration of the difference in average daily urinary iodine losses encountered in goitrous and nongoitrous regions,[18] as well as the quantity of iodine estimated as necessary to maintain normal iodine metabolism.[13, 35] The *optimal* daily requirement appears to be about 3 micrograms per kilo or 200 micrograms for the 70 Kg. adult.[13, 35]

If iodine feeding is essential under normal conditions of stress and strain, then it becomes twice as significant to the pregnant woman or to the lactating mammal. The loss of iodine in the milk results in depletion of the mother's iodine reserve with an ensuing negative balance. This loss should be compensated by a sufficiently large, previously built-up iodine reserve or by a stable increased intake. Otherwise, iodine deficiency goiter may develop.[29, 58, 59] Moreover, as supplemental iodine is administered, more becomes available to the young through the mother's milk.[31, 65, 70]

For full efficacy iodine prophylaxis should begin as early as possible, especially before the age of puberty. Consequently, it would seem wisest to commence prophylaxis even before the time of conception and to maintain it throughout pregnancy. It should be continued as well during childhood and *particularly through the menarche* in young girls.

Various methods of supplying supplemental iodine to the inhabitants of iodine-deficient areas have been advanced. These include the consumption of foods known to be rich in iodine, iodinization of water supplies, administration of iodine at regular intervals in the form of solutions or tablets, the consumption of milk with an increased iodine content, and the general use of iodized salt. The use of iodized salt, because of its ready preparation, its low cost, and its common employment in cooking or seasoning, has thus far proved the most widely adopted method.

Iodine supplementally administered in the form of iodized salt, when thus extensively used, has repeatedly proved beneficial in the prevention of endemic goiter. Its curative effect, however, depends on the character of the goiter, as well as on the age at the time iodine treatment is instituted.

In its early stages, simple goiter is readily controllable. As long as the gland is in a state of compensatory hyperplasia, administration of iodine can induce a regression of the glandular enlargement. Daily doses of sodium or potassium iodide, 10–15 mg. on alternate months for one year; syrup of hydriodic acid, 1 cc. daily; or 0.5 Gm. iodostarine or iodocasein are among the many therapeutic procedures which have been employed. A maximum reduction in the size of the goiter will occur after approximately one year's treatment or less.

While iodine therapy is of value to patients with colloid goiter little beneficial change may be expected in older patients with goiters of long standing in which have developed extensive pathologic alterations such as hemorrhage with resultant cyst formation, calcification, vascular degenerative changes, and old nodular formations.[29, 72] If the goiter is not nodular, however, iodine therapy is worthy of trial. Also, the administration of desiccated thyroid, 0.06 Gm. daily, for at least one year, by reducing the activity of the thyroid gland should tend to cause a regression in its size. Surgical removal of a diffuse colloid goiter is but rarely indicated, and then only when there is sufficient disfigurement or the development of pressure symptoms.

In cretinism, treatment is encouraging but not always wholly successful,[5, 37, 43] despite the availability of a satisfactory replacement therapy for the diminished secretion of the thyroid gland. Prevention, by the administration of sufficient iodine to expectant mothers, is by far the simpler and more successful course. Once a cretin is born, the extent of subsequent improvement depends upon the promptness and adequacy of thyroid administration. The prognosis for subsequent normal growth and physical development, with early and intensive treatment, is good. Delay in growth caused by thyroid deficiency before treatment is started cannot be recovered.[43]

The final mental age attained by the cretin depends upon the duration of the thyroid deficiency before treatment was instituted and upon the age at which the deficiency began. With adequate thyroid therapy (0.06 to 0.13 Gm. daily) a small number of the children will achieve normal intelligence, while most of the others should turn out to be useful citizens, with sufficient mental capacity to earn a living.[43]

Evident microscopic changes ordinarily occur in hyperplastic thyroids after the administration of supplemental iodine. Rapid involution of an existing hyperplasia is usually induced; moreover, glandular hyperplasia of the residual tissue, even after extirpation of as much as three-fourths of the thyroid, can be prevented by the administration of sufficient iodine postoperatively. It has been observed that a hyperplastic gland cannot revert to the colloid state without the availability of a necessary minimum of iodine.[64]

Despite almost worldwide favorable results, thus empirically substantiating the basic theory behind iodine prophylaxis, objections have been repeatedly raised, in the earlier years abroad and more recently in the United States, to the preventive use of supplemental iodine.[50, 76] This concern over *Jodbasedow*, or "iodine-induced hyperthyroidism," arose as early as 1820, when Coindet[7] treated his patients with excessive amounts of iodine, and has continued for many years along with the subsequent progress of iodine prophylaxis.

Convincing proof is lacking that iodine-induced hyperthyroidism commonly results from the administration of increased amounts of iodine to goitrous patients. On the contrary, the evidence furnished by Kimball's data,[48] shows that only 4 per cent of those patients with goitrous "adenomas" using iodized salt later developed symptoms of hyperthyroidism, as compared with 56 per cent of individuals similarly afflicted who took no form of iodine supplement.

In current medical practice there is ordinarily but little hesitancy in prescribing relatively large amounts of iodide, even in specific nonthyroid indications, without any special regard to the thyroid gland and its activity. Demonstrably harmful effects as a result of subsequent increased thyroid function are not expected and are but rarely encountered. At most there occurs in certain individuals a reaction known as *iodism* and characterized by symptoms varying from a mild coryza or a moderate acne to a severe febrile dermatitis.[83]

No ill results are to be anticipated from the widespread use of iodides in the minute concentration in which they occur in iodized salts or from diets rich in iodine-containing foods. Instead, it is confidently expected that, with the nearly worldwide preventive use of iodine, the general decrease in the incidence of goiter noted, prior to the recent devastating war, throughout most of Europe, New Zealand, and the United States, will continue unchecked and will even penetrate further into other parts of the world.

To thrive and function at his best under the ever-increasing demands of modern effort and production each individual should have, among other important elements, an adequate supply of iodine. Iodine is not only a nutritional necessity in the prevention of goiter and endemic cretinism, but also plays an important role in the well-being of all mammals. The increased physical activity and emotional stress resultant from present world tensions put increased demands upon the human body. An optimal response to these demands cannot be maintained without a sufficient supply of iodine.

BIBLIOGRAPHY

1. Albert, A., Rawson, R. W., Merrill, B. L., and Riddell, C. Reversible inactivation of thyrotropic hormone by elemental iodine. *J. Biol. Chem.* 166:637, 1946.
2. Baumann, E. Ueber den Jodgenhalt der Schilddrüsen von Menschen und Thieren. *Ztschr. f. physiol. Chem.* 22:1, 1896.
3. Betheil, J. J., Wiebelhaus, V. D., and Lardy, H. A. Studies of thyroid toxicity, I.: A nutritional factor which alleviates the toxicity of ingested thyroid substance. *J. Nutrition* 34:431, 1947.
4. Boothby, W. M. The basal metabolic rate in hyperthyroidism. *J.A.M.A.* 77:252, 1921.
5. Brown, A. W., Bronstein, I. P., and Kraines, R. Hypothyroidism and cretinism in childhood. *Am. J. Dis. Child.* 57:517, 1939.
6. Cameron, A. T. Recent Advances in Endocrinology, (ed. 3). Philadelphia, Blakiston, 1936.
7. Coindet, J. R. Découverte d'un nouveau remède contre le goître. *Ann. de chim. et phys.* 15:49, 1820.
8. Cole, V. V., and Curtis, G. M. Cyclic variations in urinary excretion of iodine in women. *Proc. Soc. Exper. Biol. & Med.* 31:29, 1933.
9. Curtis, G. M. Iodine metabolism in toxic goiter. *J. Med.* 15:148, 1934.
10. Curtis, George M., Cole, V. V., and Phillips, F. J. Blood iodine in thyroid disease. *West J. Surg.* 42:435, 1934.

11. Curtis, George M., and Fertman, M. Been. An analysis of the blood iodine in thyroid disease. *Arch. Surg.* 50:207, 1945.
12. Curtis, G. M., and Fertman, M. B. The relation of the basal metabolic rate to the blood iodine in thyroid disease. *Ann. Surg.* 122: 963, 1945.
13. Curtis, G. M., and Fertman, M. B. "Iodine in nutrition." Chapter VIII of the *Handbook of Nutrition.* Chicago, A.M.A., 1943, pp. 150-151.
14. Curtis, G. M. and Fertman, M. B. The blood iodine in nonthyroid disease. *Arch. Surg.* 54:541, 1947.
15. Curtis, G. M., and Puppel, I. D. Increased urinary excretion of iodine in hyperthyroidism. *Arch. Int. Med.* 60:498, 1937.
16. Curtis, G. M., and Puppel, I. D. Urinary iodine in thyroid disease. *West. J. Surg.* 45:417, 1937.
17. Curtis, G. M., and Puppel, I. D. The iodine metabolism in thyroid disease. Trans., Third International Goiter Conference, Washington, D. C., 1938, p. 367
18. Curtis, G. M., Puppel, I. D., Cole, V. V., and Matthews, N. L. The normal urinary iodine of man. *J. Lab. & Clin. Med.* 22:1014, 1937.
19. Curtis, G. M., and Swenson, R. E. The protein-bound blood iodine in patients with nontoxic nodular goiter. *Trans. Am. Goiter Assn.*, 145, 1947.
20. Curtis, G. M., and Swenson, R. E. The significance of the protein-bound blood iodine in patients with hyperthyroidism. *Ann. Surg.*, 128:443, 1948.
21. Davis, C. B., Curtis, G. M., and Cole, V. V. The normal iodine content of human blood. *J. Lab. & Clin. Med.* 19:818, 1934.
22. Davison, R. A., Zollinger, R. W., and Curtis, G. M. The fractionation of the blood iodine I.: Findings in patients with normal thyroid function and with hypothyroidism. *J. Lab. & Clin. Med.* 27:643, 1942.
23. DeCourcy, J. L. Iodine metabolism, normal and abnormal: Its relation to the reticulo-endothelial system. *Trans. Am. A. Study Goiter*, p. 133, 1937.
24. DeCourcy, J. L. Further study of blood iodine changes in affections of the gallbladder. *Surg., Gyn. & Obs.* 65:180, 1937.
25. DeCourcy, J. L. Iodine content of blood in cholecystic disease. *Arch. Surg.* 35:140, 1937.
26. DeRobertis, E., and Nowinski, W. W. The proteolytic activity of normal and pathological human thyroid tissue. *J. Clin. Endocrinol.* 6:235, 1946.
27. DeRobertis, E. The mechanism of the therapeutic effect of iodine on the thyroid gland. *Science* 103:421, 1946.
28. Eggenberger, H. "Kropf und Kretinismus." *Hirsch' Handbuch der inneren Sekretion*, 3; Numbers 3 and 4, Leipzig, Kabitsch, 1927.
29. Elmer, A. W. Iodine Metabolism and Thyroid Function. New York, Oxford, 1938.

30. Enright, Lena, Cole, V. V., and Hitchcock, F. A. Basal metabolism and iodine excretion during pregnancy. *Am. J. Physiol.* 113:221, 1935.

31. Von Fellenberg, T. Das Vorkommen, der Kreislauf und der Stoffwechsel des Jods. *Ergebn. d. Physiol.* 25:176, 1926.

32. Fenger, F., Andrew, R. H., and Vollertson, J. J. Geographic location and the iodine content of the thyroid gland. *J. Am. Chem. Soc.* 53:237, 1931.

33. First Official Report of the Goiter Survey of Michigan: Study of the Effect of the Use of Iodized Salt on the Incidence of Goiter. *J. Michigan M. Soc.* 36:647, 1937.

34. Flagge, C. H. On sporadic cretinism, occurring in England. *Med. Chir. Trans.* 54:155, 1871.

35. Flickinger, F. M. The Iodine Requirement of Man. Thesis for M. S. Degree, Dept. Surg. Res., Ohio State University, 1941.

36. Gaddum, J. H. Quantitative observations on thyroxine and allied substances. *J. Physiol.* 64:246, 1927.

37. Gesell, A., Amatruda, C. S., and Culotta, C. S. Effect of thyroid therapy on the mental and physical growth of cretinous infants. *Am. J. Dis. Child.* 52:1117, 1936.

38. Hanzlik, P. J., Talbot, E. P., and Gibson, E. E. Continued administration of iodide and other salts: Comparative effects on weight and growth of body. *Arch. Int. Med.* 42:579, 1928.

39. Harington, C. R., and Barger, G. Chemistry of thyroxine; Constitution and synthesis of thyroxine. *Biochem. J.* 21:169, 1927.

40. Hercus, C. E., and Roberts, K. C. The iodine content of foods, manure and animal products in relation to the prophylaxis of endemic goiter in New Zealand. *J. Hyg.* 26:49, 1927.

41. Hunziker, H. Kropf und Längenwachstum. *Schweize med. Wchnschr.* 50:209, 1920.

42. Hunziker, H., and Wyss, V. M. Ueber systematische Kropf-Therapie und prophylaxe. *Schweiz. med. Wchnschr.* 3:49, 1922.

43. Hurxthal, L. M., and Musulin, N. Cretinism: Definition, classification and etiology. *Am. J. Med.* 1:56, 1946.

44. Justus, J. Ueber den physiologischen Jodgehalt der Zelle. *Virchows Arch. f. path. Anat.* 170:500, 1902.

45. Kalkus, J. W. A study of goiter and associated conditions in domestic animals. Bull. 156, Washington State Expt. Sta., 1920.

46. Kendall, E. C. Isolation in crystalline form of the compound containing iodine which occurs in the thyroid; Its chemical nature and physiological activity. *Trans. Ass'n Am. Phys.* 30:420, 1915.

47. Kendall, E. C., and Simonsen, D. G. Seasonal variations in the iodine and thyroxin content of the thyroid gland. *J. Biol. Chem.* 80:357, 1928.

48. Kimball, O. P. The efficiency and safety of the prevention of goiter. *J.A.M.A.* 91:454, 1928: The prevention of goiter in Michigan and Ohio. *ibid.* 108:860, 1937.

49. King, J. D. The Iodine Content of the Normal Thyroid Gland Correlated with Its Histology and the Iodine Content of Other Normal Body Tissues in Central Ohio. Dissertation for Ph.D., Dept. Surg. Res., Ohio State University, 1940.

50. Kocher, T. Die Therapie des Kropfes. *Deutsche Klin.* 8:1115, 1904: Ueber Jodbasedow. *Arch. f. klin. Chir.* 96:403, 1910.

51. Leblond, C. P., Puppel, I. D., Riley, E., Radike, M., and Curtis, G. M. Radioiodine and iodine fractionation studies of human goitrous thyroids, *J. Biol. Chem.* 162:275, 1946.

52. Libecap, I. L. The Iodine Content of Normal Human Tissues. Thesis for M.M.Sc., Dept. Surg. Res., Ohio State University, 1942.

53. Lipsett, M. B., and Winzler, R. J. Effects of vitamin A deficiency on thyroid function studied with radioactive iodine. *Endocrinology* 41:494, 1947.

54. McCarrison, R. The interaction of food and sanitary conditions in the causation and prevention of thyroid disease. *Indian J. M. Research* 20:957, 1933.

55. McClendon, J. F. Iodine and the Incidence of Goiter. Minneapolis, Univ. Minnesota Press, 1939.

56. McClure, R. D. Thyroid surgery in southern Michigan as affected by the generalized use of iodized salt. *J. Michigan M. Soc.* 33:58, 1934: The incidence of operations for goiter in southern Michigan: Effect of iodized salt after twelve years' general use. *J.A.M.A.* 109:782, 1937.

57. Marine, D. On the occurrence and physiological nature of glandular hyperplasia of the thyroid (dog and sheep), together with remarks on important clinical (human) problems. *Bull. Johns Hopkins Hosp.* 18:359, 1907.

58. Marine, D. Studies on the etiology of goiter, including Graves' disease. *Ann. Int. Med.* 4:423, 1930.

59. Marine, D. The importance of relative iodine deficiencies in certain forms of goiter. *J. Am. Dietet. Assn.* 9:1, 1933.

60. Marine, D. Physiology and principal interrelations of the thyroid. *J.A.M.A.* 104:2250, 1935.

61. Marine, D. The pathogenesis and prevention of simple or endemic goiter. *J.A.M.A.* 104:2334, 1935.

62. Marine, D. and Kimball, O. P. Prevention of goiter in man. *J.A.M.A.* 77:1068, 1921.

63. Marine, D., and Lenhart, C. H. Effects of the administration or the withholding of iodine-containing compounds in normal, colloid or actively hyperplastic (parenchymatous) thyroids of dogs. *Arch. Int. Med.* 4:253, 1909.

64. Marine, D., and Lenhart, C. H. Further observations of the relation of iodine to the structure of the thyroid gland in the sheep, dog, hog and ox. *Arch. Int. Med.* 3:66, 1909.
65. Matthews, N. L., Curtis, G. M., and Meyer, J. H. The effect of increased iodine feeding on the iodine content of cows' milk. *J. Dairy Res.* 10:395, 1939.
66. Maurer, E., and Ducrue, H. Zur Kenntnis des Jods als biogenes Element: Der Jodgehalt im normalen tierischen Organismus. *Biochem. Ztschr.* 217:227, 1930.
67. Maurer, E., and Diez, S. Zur Kenntnis des Jods als biogenes Element: Ueber Wachstumsbechleunigung an jungen Ratten bei Vertfütterung jodangereicherter Kost an das laktierende Muttertier. *Biochem. Ztschr.* 182:291, 1927.
68. Means, J. H. The Thyroid and Its Diseases. Philadelphia, Lippincott, 1937.
69. Means, J. H., and Richardson, E. P. The Diagnosis and Treatment of Diseases of the Thyroid. New York, Oxford, 1938.
70. Meyer, J. H. The Iodine Content of Milk. Thesis for M. S., Dept. Surg. Res., Ohio State University, 1940.
71. Norris, H. Notice of a remarkable disease, analogous to cretinism, existing in a small village in the west of England. *Med. Times,* 17: 257, 1848.
72. Orr, J. B., and Leitch, I. Iodine in Nutrition. Medical Research Council Special Series Report No. 123, London, 1929.
73. Perlman, I., Morton, M. E., and Chaikoff, I. Radioactive iodine as an indicator of the metabolism of iodine. *J. Biol. Chem.* 139:433, 449, 1941.
74. Phillips, F. J., Erf, O., and Curtis, G. M. The effects of prolonged increased iodine feeding. *Ohio J. Science* 35:286, 1935.
75. Plummer, H. S. Results of administering iodine to patients having exophthalmic goiter. *J.A.M.A.* 80:1955, 1923.
76. de Quervain, F. Report of the Second International Goiter Conference. Berne 1933, pp. 10-12.
77. Rawson, R. W., Moore, F. D., Peacock, W., Means, J. H., Cope, O., and Riddell, C. B. Effect of iodine on thyroid gland in Graves' disease when given in conjunction with thiouracil: Two-action theory of iodine. *J. Clin. Investigation* 24:869, 1945.
78. Remington, R. E., Coulson, E. J., and Levine, H. The antigoitrogenic value of some foods. *J. Nutrition* 12:27, 1936.
79. Remington, R. R., and Levine, H. Studies on the relation of diet to goiter. III: Further observations on a goitrogenic diet. *J. Nutrition* 11:343, 1936.
80. Report of the Initial Meeting of the Study Committee on Endemic Goiter of the American Public Health Association, Detroit, June 14-15, 1941.
81. Robertson, R. Cecil. The problem of endemic goiter in Yunnan province. *J. Clin. Endocrinol.* 1:285, 1941.

82. Robinson, Margaret. Hormones and lactation: Dried thyroid gland. *Lancet* 2:385, 1947.

83. Salter, W. T. The Endocrine Function of Iodine. Cambridge, Mass., Harvard, 1940.

84. Shepperd, J. H. The northern pig, its habits, breeding and management. Bull. 230, North Dakota Agr. Expt. Sta., 1929.

85. Sharples, G. R., Pearsons, J., and Prato, G. Production of goiter in rats with soy bean flour. *J. Nutrition* 17:545, 1939.

86. Shore, R. A., and Andrew, R. L. Goiter in school children: The incidence of goiter in school children in relation to the amount of iodine in soil and water in certain districts of the north island in New Zealand. Dept. Health & Sc. & Ind. Research, Wellington, *Bull Hyg.* 5:94, 1930.

87. Shelton, E. K. Hypothyroidism in childhood. *J.A.M.A.* 117:1948, 1941.

88. Simkins, S. Use of massive doses of vitamin A in the treatment of hyperthyroidism. *J. Clin. Endocrinol.* 7:574, 1947.

89. Sturm, A., and Buchholz, B. Beiträge zur Kenntnis des Jodstoffwechsels: Jodverteilung im menschlichen und tierischen Organismus in ihrer Beziehung zur Schilddrüse. *Deutsch. Arch. f. klin. Med.* 161:227, 1928.

90. Welch, J. Hairlessness and goiter in newborn domestic animals. Bull. 119, Montana Agr. Expt. Sta., 1917.

91. Weston, W. Specially produced milk in the solution of the goiter problem. *South. M. J.* 27:249, 1934.

Chapter 14

THE ESSENTIAL TRACE ELEMENTS

Carl V. Moore, James Innes, and Elizabeth M. Innes

TRACE elements are elements which are found in animal tissues in minute amounts. Five are known to be essential to animal life: copper, cobalt, fluorine, manganese, and zinc. Many other minerals—aluminium, arsenic, boron, caesium, chromium, lead, lithium, molybdenum, rubidium, selenium, silicon, silver, strontium, tellurium, tin, titanium, and vanadium—are also frequently found in traces in animal tissues.[39, 89, 126, 136] There is no convincing evidence, however, that they are necessary to life; they may merely be accumulated in tissues because they are present in food. Some of these minerals may be shown to be indispensable when methods of study become less crude, but at present they are of medical interest largely because they may accumulate in toxic amounts. Discussion, therefore, will be limited to the five known to be nutritionally important: copper, cobalt, fluorine, manganese, and zinc.

Even the information about these five essential trace elements, however, is extremely fragmentary, particularly with reference to man. Proof that any element is essential to life depends largely on the demonstration that when it is deficient, certain signs or metabolic defects result and that these abnormalities can be corrected by replacement therapy. Experiments on animals have provided these data for copper, manganese, and zinc. The amounts of cobalt needed are so minute that no one has been able to prepare a diet capable of producing cobalt deficiency in the laboratory. Fortunately, the soil in some parts of the world contains so little cobalt that animals which feed on the vegetation of these regions become specifically deficient. Depletion of cobalt, manganese, and zinc of a sufficient degree to cause disturbances of health have not been recognized in man. On rare occasions, copper deficiency has been demonstrated in infants. Inadequacies of fluorine have been shown to increase the incidence of dental caries.

Most of the information about essential trace elements has been derived from experiments on animals and many of the data have not yet been related to disease in the human. An attempt will be made, however, to emphasize those observations which seem to have the most definite clinical implications.

COPPER

The amount of copper in the adult human body has been estimated to be about 100 to 150 mg. Evidence, obtained mainly from animal experiments, indicates that it is concerned in some way with the synthesis of hemoglobin in the bone marrow,[59] with the formation and maintenance of compounds having enzymatic activity,[110, 112] with central nervous system physiology,[49] and with some forms of pigment metabolism.[61] Occurrence of deficiency in man is unlikely because the metal is widely distributed in food and the requirements for it are low. In rare cases of hypochromic anemia in infancy, a more satisfactory therapeutic response may occur when copper is added to iron therapy, but no other evidences of copper deficiency have been recognized in man. A review dealing with many of the biologic aspects of copper, with particular reference to its role in hematopoiesis, was published by Cartwright in 1947.[17]

METABOLISM AND HUMAN REQUIREMENTS

Much is lacking in our knowledge of copper metabolism. It appears that the metal is absorbed largely from the upper portion of the small intestine[108] and is transported by the blood to organs of storage, utilization, or excretion.[107, 108, 110] It is present both in plasma and in the red cells, the average human serum content being estimated at 116 micrograms per 100 cc. in adult males and 131 micrograms per 100 cc. in adult females.[18] In experiments in which radioactive copper was fed to normal dogs,[148] the metal appeared quickly in the plasma with a peak concentration appearing in from two to five hours, after which the level fell abruptly. Demonstrable amounts were still present after two days. Radioactive copper likewise appeared rapidly in the circulating red blood cells with a slow increase in its concentration over a two-day period. The up-take was found to be greater in dogs in which hematopoietic activity had been accelerated by bleeding.

Copper is widely distributed in animal tissues; highest concentrations occur in the liver and central nervous system. Eggleton reports the following amounts of copper in milligrams per Kg. of dry weight of human tissues: liver, 40.2; cerebellum, 28.8; cerebrum, 18.1; kidney, 14.1; heart, 13.4; pancreas, 8.7; and muscle 6.4.[40] The liver of newborn animals contains more copper than the liver of adults of the same species; this is also true in man. It would appear that the extra copper is intended to act as a reserve during the nursing period when the intake is low. Certain types of tumor tissue have been shown to have a marked affinity for copper storage.[57] Animal experiments have shown that radioactive copper can be found in the bone marrow within a short time of administration.[113] Some of the copper in tissues is combined with protein to form compounds possessing enzymatic activity, and in rat tissues the formation and maintenance of cytochrome oxidase and catalase activity are dependent on an adequate copper intake.[110, 112]

The question of copper utilization can best be discussed when the manifestations of copper deficiency are considered. The metal is excreted from the body by the bowel and to a lesser extent by the kidneys.[58] With a daily intake of 2.17 mg., the twenty-four-hour excretion of copper in man is around 1.22 mg. in the feces and 0.27 mg. in the urine.[58] Van Ravesteyn has studied the elimination of copper following the daily oral administration of 150 mg. of copper sulphate to normal adults for three days. Of the copper given 65 to 75 per cent could be recovered from the feces during the first six to nine days, and it was noted that the copper content of the bile rose to more than twice its normal level during this period. No increased urinary excretion of the metal was observed, but the copper content of the stools remained at a level of 1 to 2 mg. per day higher than during a control period. This suggests that the 25 per cent of the dose of copper originally absorbed was gradually being eliminated by the bowel. Further studies by the same worker, using intravenous injections of copper, indicated that in addition to the copper excreted through the bile, there may be some direct elimination by the alimentary tract.[102]

Approximate estimates have been made of the daily human requirements for copper. It has been stated that boys between the ages of 3 and 6 years need from 0.053 to 0.085 mg. per Kg. of body weight,[117] and adults, 2.0 mg. daily.[20] The Food and Nutrition Board of the National Research Council recommended in 1942 that "the requirement for copper for adults is in the neighborhood of 1.0 to 2.0 mg. a day. Infants and children require approximately 0.05 mg. per kilogram of body weight.

The requirement for copper is approximately one-tenth that for iron."[93] The average daily intake of copper by adults has been estimated by Thompsett as from 2.0 to 2.5 mg.,[135] and Wintrobe states that it may vary from 1 to 7 mg.[145]

Copper Deficiency

IN ANIMALS

The first experimental evidence that copper is an essential element was provided in 1928 when Hart and his co-workers at the University of Wisconsin showed that hypochromic anemia develops in animals fed a diet deficient in copper even though adequate amounts of iron are present.[59] Weanling white rats were made deficient in both copper and iron by being fed a milk diet which carefully avoided contamination with metals. The animals developed a hypochromic anemia which did not respond to iron therapy unless copper was also provided. The amounts necessary were exceedingly small; 5 micrograms per day were enough to initiate and maintain a steady formation of hemoglobin, but a more rapid response was obtained with larger amounts. This observation has since been confirmed many times and has been found to hold also for rabbits[119] and dogs.[82] It has been shown that although iron can be absorbed and stored normally in the absence of copper, it cannot be utilized by the bone marrow unless the latter element is present. In animals and human subjects who are deficient in iron but *not* in copper, the copper in blood is increased as if it were mobilized and waiting in readiness for use whenever iron might become available. The exact role of copper in effecting an increase of hemoglobin synthesis is not known. It is not in itself a component of the hemoglobin molecule nor of the structural material of erythrocytes. The most acceptable explanation seems to be that offered by Schultze. He has found that in pure copper deficiency the cytochrome oxidase activity in bone marrow is low; whereas in animals which have adequate copper but are deficient in iron, the cytochrome oxidase activity in the marrow is increased.[110-112] He postulates, therefore, that the stimulating effect of copper on iron utilization may be due to its function in forming and maintaining cytochrome oxidase.

Some other functions of copper have been recognized, but their relationship, if any, to the question of erythropoiesis is only speculative. The oxidation of glutathione is accelerated in the presence of small amounts of copper[139] and it has been observed that during recovery from hemorrhagic anemia the glutathione content of the blood is increased.[10] The catalytic effect of copper on the oxidation of cysteine[40] and of ascorbic acid[144] has been described. In guinea pigs the addition of copper to a scorbutic diet has been reported to prevent the appearance of signs of scurvy.[14, 79] Glycolysis is known to be activated by copper[144] and is accelerated in anemia.

During recent years, copper deficiency has been studied in connection with a disease in lambs found particularly in certain parts of Australia and Britain. It has been given descriptive names like "enzootic ataxia" and "swayback." The condition is a paralytic disease of newborn and young lambs, with pathologic lesions in the central nervous system consisting of demyelination and degeneration of the motor tracts. In Britain it occurs in lambs born from apparently healthy ewes which have been in an "affected area" for more than one year.[70, 71] In Australia, it has been reported that the ewes develop a severe macrocytic anemia and that both ewes and lambs have amounts of copper in their blood and liver much below normal.[8] All attempts to transmit the disease experimentally have failed, but the condition can be prevented by giving copper supplements to ewes during pregnancy.[7, 8, 36] It is evident, however, that there are still many puzzling features regarding swayback which have never been satisfactorily explained. Evidence is fairly convincing that the disease in Australia is caused by a copper deficiency but in Britain it has been observed in areas where the pasture has a normal copper content. Under these circumstances, therefore, there may be some other factor which interferes with the absorption or utilization of copper. Observations by Ferguson, *et al.* indicate that the presence of molybdenum in the diet may actively interfere with copper metabolism.[46] The pathogenesis of swayback is thus one of complexity; whatever the causative factors may be, they act on the developing myelin of the fetal lamb with great severity at a time when myelination is at the height of its activity. An interesting and confusing observation is that 4 of 7 individuals who worked intensively in the research on swayback were found to have developed a disease of the central nervous system which was clinically indistinguishable from disseminated sclerosis.[16] There is little knowledge regarding the danger of prolonged administration of copper salts, but it probably is not without risk. In sheep, an excess of copper produces intravascular hemolysis, anemia, and jaundice, preceded by a very definite rise in the blood copper level.[2]

Another function of copper is related to certain phases of pigment metabolism. The fur of black or piebald rats becomes gray after the animals have been placed on a diet deficient in copper. This graying is not affected by the administration of the recognized achromotrichia factors of the vitamin B complex such as pantothenic acid.[61] The ink sac of the octopus contains a large amount of copper, although the melanic pigment in the ink itself contains only a small amount of the metal. It has been suggested that copper functions by catalyzing the oxidation of the precursor of melanin.[26] This furnishes, therefore, a further example of the catalytic or enzymatic activity of copper. It is interesting to note also that hemocyanin, the oxygen-carrying blood pigment of marine blue-bloods, the gastropods and arthropods, contains copper.[104]

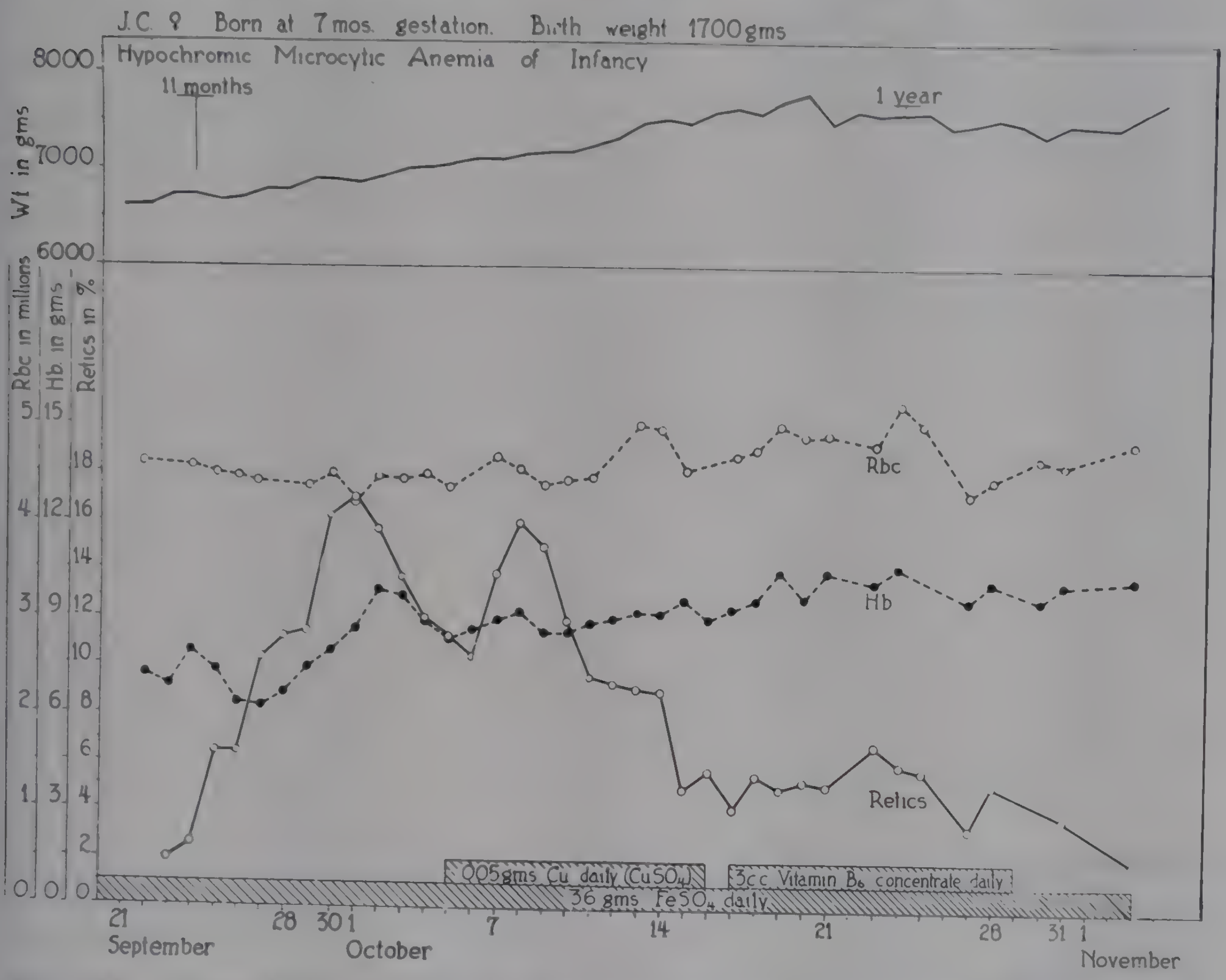


FIG. 21. Secondary reticulocyte response produced by copper in the treatment of nutritional anemia of infancy.

IN MAN

If copper deficiency ever occurs in adults, it has never been recognized. Several clinical investigators have reported that the combined administration of copper and iron in the treatment of hypochromic anemia is more effective than is iron alone, or that an occasional patient will not respond to iron therapy unless copper is added. This literature has been reviewed by Hutchinson,[69] Segard,[120] and Schultze.[110] Acceptable control studies are lacking in many of these reports and the supporting hematologic data are not convincing. Other workers have not been able to obtain similar results.[28, 51]

There are certain cases of hypochromic anemia in infancy, however, in which the therapeutic efficacy of iron seems to be augmented when copper is given.[44, 87] One of us (C.V.M.) has observed several such infants in whom a second reticulocyte peak occurred when copper was added to ferrous sulphate after iron alone had induced an initial response (Fig. 21). This was interpreted as indicating that copper probably had an additive effect, but the rate of hemoglobin regeneration was not detectably accelerated.

Since the human requirement for copper is small and the element is so widely distributed in food, it is difficult to imagine circumstances under which copper deficiency might develop except during infancy. The copper content of human milk is probably higher than that of cow's milk, but that of both is low.[110] Before supplementary feedings are begun, the infant's intake of the metal may conceivably be inadequate.

The diagnosis of copper deficiency must be made on the basis of exclusion. If a patient with hypochromic anemia does not respond satisfactorily to iron therapy until copper also is given, then a deficiency of the latter metal is presumably present. It must be remembered, however, that the hemoglobin rise stimulated by iron does not begin for about seven days and then proceeds at the rate of from 0.15 to 0.3 Gm. of hemoglobin per 100 cc. per day. The response to iron alone should not be called inadequate until a fair trial has been given. Care should also be taken to make certain that fever and infection are not interfering with the utilization of iron.

From 1 to 5 mg. of copper as copper sulphate is an adequate daily dose. Elvehjem and his associates[44] have recommended that when copper is given therapeutically, the Fe:Cu ratio should be kept at approximately 25. Large doses are toxic and should be avoided. The routine practice of giving copper and iron together in the treatment of all patients with hypochromic anemia is unnecessary and should be discouraged.

COBALT

Deficiency of cobalt has never been recognized in man and probably does not occur. The requirement for cobalt is so low that experimental production of a deficiency has never clearly been accomplished. In some parts of the world, however, the soil contains so little of the metal that cattle and sheep raised on these lands become deficient and develop a disease which is fatal unless cobalt is provided. Cobalt's right to be considered an essential trace element rests on this evidence and in the recent demonstration that it is a part of the vitamin B_{12} molecule.[106a, 127b] It is of interest that inadequacies of cobalt cause an anemia, while the feeding of relatively small amounts to many species of animals induces a polycythemia.

METABOLISM AND REQUIREMENT

Vitamin B_{12} is the only cobalt-containing compound of natural origin which has so far been isolated from animal tissues. Current evidence indicates that it probably is the anti-pernicious anemia principle in liver, capable of inducing hematologic, neurologic, and general clinical remissions in patients with pernicious anemia.[8c, 8d, 57a, 127a, 144a, 144b] In many cases, the material is effective in doses as small as 1 microgram per day when given parenterally. While it is also a potent therapeutic agent for nutritional macrocytic anemia and tropical sprue,[130a] instances have now been reported of macrocytic anemia of pregnancy[8a, 30d] and of megaloblastic anemia of infancy[80a] which were refractory to vitamin B_{12} but which responded to folic acid. An inadequate amount of cobalt is not the factor which precipitates vitamin B_{12} deficiency; patients with pernicious anemia do not respond to the administration of cobalt.

Vitamin B_{12} is poorly absorbed from the intestinal tract of man unless given in conjunction with normal human gastric juice.[8b, 57b] This and other related observations suggest that vitamin B_{12} is probably Castle's extrinsic factor as well as the antipernicious anemia principle. Finally, there is a growing body of evidence which indicates that vitamin B_{12} is closely related to the animal protein factor.[97a] The relationship, if any, of this interesting substance to pteroyl glutamic acid, and its biochemical function are unknown. Whether cobalt has any biologic function other than as a component of vitamin B_{12} is also unknown.

Cobalt is required in such small amounts that the minimum need has never been defined. Rats fed a basal ration which provided only 0.03 microgram of cobalt per rat per day showed no evidence of cobalt deficiency.[64] The basal requirement of cows has been estimated at about 1 mg. per day.[94]

Experiments with radioactive cobalt[23, 54, 123] have shown that when small amounts (10 micrograms) are fed to rats about 40 per cent is absorbed. Very little of the absorbed cobalt, or very little of that given parenterally, is retained. The chief path of excretion is in the urine and a portion of the small fraction eliminated by the bowel comes from bile. Highest tissue concentrations develop in the glandular organs, particularly the pancreas, liver, spleen, and kidneys.

A number of foodstuffs have been analyzed and found to have a cobalt content varying from 6 to 47 micrograms per 100 Gm. of dry weight.[1]

COBALT DEFICIENCY

Cobalt deficiency has been recognized in sheep and cattle which feed from pasture deficient in the metal.[17, 136] Manifestations of the disease differ slightly in various geographic areas, but in general are as follows: impaired growth, listlessness, abnormalities of the coat, anorexia, progressive emaciation, weakness, and varying degrees of anemia. The disease has been known by many names: enzootic marasmus, Denmark disease, coast disease, Bush sickness, salt sick, pine, Lake Shore disease and Nakuritis. It has been observed in parts of Australia, New Zealand, Kenya, Scotland, Florida, Michigan, and Wisconsin. Livers of affected animals are deficient in cobalt. Hemosiderosis, found in the liver, spleen, and kidneys, tends to disappear when hemoglobin regeneration is stimulated by cobalt administration. Cures are produced with doses of 1 to 2 mg. of cobalt per day. The disease may be prevented either by giving 0.1 mg. daily to sheep and 0.3 mg. daily to cattle or by treating the soil with a dressing of 0.5 lb. of cobalt acetate per acre.

Two observations have been confusing: (1) the disease can also be treated successfully with liver but not with liver ash;[47, 126] and (2) it does not occur in horses and pigs pasturing on the same deficient areas.[136] Both of these may possibly be explained by the demonstration that cobalt is curative only when given by mouth and not when given by injection.[84] This suggests that organisms in the rumen of sheep and cattle may synthesize some essential nutrient, presumably vitamin B_{12}, but can do so only when cobalt is available. If this interpretation is correct then the deficiency manifestations described above may be those of vitamin B_{12} (or animal protein factor) deficiency.

Effects of Feeding Cobalt

Administration of small amounts of cobalt causes a polycythemia in rats, dogs, rabbits, guinea pigs, mice, frogs, and chickens.[110] The erythrocytosis is the result of a true polycythemia and is not due to a decreased blood volume.[96] The bone marrow becomes hyperplastic and a reticulocytosis develops. Only 0.04 to 0.05 mg. of cobalt in the entire body of a rat is sufficient to produce a decided elevation in the red blood cell count. The polycythemia does not occur in splenectomized rats nor when the diet is deficient in iron or in copper.[17] Many substances have been reported to counteract the polycythemia-producing effects of cobalt: ascorbic acid, manganese, concentrated liver extract, ventriculin, whole beef, and whole liver.[17] In rats, 40 mg. of cobalt per kilogram of body weight must be given orally per day to produce the same degree of polycythemia as is induced by 2.5 mg. per Kg. subcutaneously per day.[131] Severe degrees of polycythemia have not been produced in the human by administration of cobalt. Three normal subjects fed 50 mg. daily as cobaltous sulphate for four weeks showed no rise in reticulocytes and no change in the erythrocyte or hemoglobin levels.[53] In another study, however, 500 mg. of cobaltous chloride given orally each day for several weeks stimulated a reticulocyte response which was followed by an increase in erythrocyte, hemoglobin and hematocrit values.[143a] It is stated that there was also an increase in the total circulating red cell mass, but no data are given. The most recent report describes the effects of giving orally 300 mg. of cobaltous chloride per day to 17 patients without anemia; a slight reticulocyte response developed within the first week in each instance. In the 10 patients who took the cobalt for over four weeks, the red cells, hemoglobin, and hematocrit rose moderately in all but one subject. The highest values observed were 6.99 million erythocytes per cubic millimeter, 18 Gm. of hemoglobin per 100 cc., and a hematocrit of 59 per cent.[8a]

The pathogenesis of cobalt polycythemia is unknown. It has been suggested that the metal may interfere with cellular oxidation in the bone marrow. The respiratory activity of animals with cobalt-induced polycythemia is not impaired,[143] but recent observations indicate that the metal inhibits the respiration of certain micro-organisms, possibly by forming partially reversible complexes between cysteine or histidine, cobalt, and oxygen.[14a] It is conceivable that such complexes form in bone marrow and produce the effect of anoxia on erythroid tissue.

Large doses of cobalt to experimental animals cause toxic manifestations characterized by a marked slowing of the growth rate, depressed erythrocytogenesis, and death. These toxic effects may apparently be neutralized by the presence in the diet of sufficient sulphur-containing amino acids or glutathione.[107] It is suggested that cobalt binds sulphydryl compounds which are needed for tissue metabolism and that a dietary excess of these substances overcomes that effect.

The stimulatory effect of cobalt on erythrocytogenesis, therefore, probably represents a pharmacologic action of the metal. As would be expected, the therapeutic possibilities of this effect have been explored. Administration of cobalt has been shown to prevent the anemia of inflammation produced in rats by the injection of turpentine.[146] It also counteracts the effect of benzol on the bone marrow in rabbits.[77] In man, the results have frequently been less conclusive.[6, 25, 142] One claim has been made that the addition of cobalt to iron in the treatment of nutritional anemia of infancy accelerated the rate of hemoglobin regeneration.[73] Weissbecker and Maurer[143a] state that 500 mg. of cobaltous chloride daily caused an erythrocytic response in some patients with anemia of chronic infection. Robinson and his associates have recently reported that the oral administration of 20 to 60 mg. of cobaltous chloride per day to nine patients with chronic suppurative disease caused a reticulocytosis which was followed by increases in red blood cell counts, in hemoglobin values, in hematocrit levels, and in total circulating hemoglobin.[106b] Berk, Burchenal, and Castle treated 20 patients with anemia of varied etiology by giving them 300 mg. of cobaltous chloride a day for 4 or more weeks.[8a] Definite reticulocyte, red cell, hemoglobin, and hematocrit rises were obtained in 2 out of 5 subjects with moderate anemia associated with infection, in 1 out of 2 patients with hypochromic anemia, and in 1 patient with Mediterranean anemia. In 3 out of 10 subjects with lymphoma, there was suggestive evidence that cobalt helped maintain higher levels of red blood cells and hemoglobin. Five patients with refractory anemia, 1 with anemia of cirrhosis, and 2 with anemia of chronic renal failure failed to respond. One of the authors of this review (C.V.M.) has treated 3 patients with refractory anemia for one to two months with daily oral doses of 50 mg. of cobalt (as cobaltous sulphate); no improvement occurred. The chief toxic symptoms experienced by human subjects to whom cobalt is given are anorexia, heartburn, nausea, and vomiting. Le Goff gave 90 mg. of cobaltous chloride daily by mouth to one patient for one hundred days, and 122 subcutaneous injections of 25 mg. each during a period of three years to another, without apparent harm.[78a] Berk and his associates gave daily oral doses as large as 1200 mg. for several weeks. Even so, information as to the toxic effects of cobalt is inadequate and caution should be used in its therapeutic trial. It would be premature to attempt a prediction of the ultimate role cobalt may have in the treatment of anemias.

FLUORINE

Fluorine has been recognized as a constituent of the skeletal system ever since Morichini in 1803 found fluorides in the bones of a fossil elephant. In 1892 Crichton-Browne suggested that the increased incidence of dental caries in England was due at least in part to a depletion of fluorine in the diet. During the early part of the present century, most of the investigations on this element were directed toward a study of its possible toxic effects. General interest was not aroused until about 1931 when it was discovered that fluorine in drinking water caused mottled tooth enamel. This observation led several communities to change their water supply so as to reduce the fluorine content to a minimum. Several years later when public health surveys were made to observe the lower incidence of mottled enamel in these population groups, the surprising discovery was made that children born after the water supply had been changed showed more dental caries than did children who had been exposed to the fluorine drinking water. Subsequent studies have confirmed this observation. Small amounts of fluorine in drinking water seem definitely to lower the incidence of dental caries. At the present time, fluorine's right to be considered an essential trace element is dependent on this observation; whether it is essential to any other function of the body is not known. Available data indicate that the optimum concentration of fluorine in drinking water to prevent dental caries is approximately 1 ppm; increased amounts cause mottling of the enamel.

Importance of Fluorine to the Teeth

1. ENDEMIC DENTAL FLUOROSIS: MOTTLED ENAMEL

Investigation of mottled enamel began in 1908 when McKay, and later Black, attempted to find out why residents of Colorado Springs were afflicted with this dental abnormality while people in adjoining communities did not show the change.[48] It was soon discovered that the teeth of those individuals who had come to Colorado Springs after enamel formation was complete were likewise free of mottling. In two communities not over four miles apart, all the native children in one town were afflicted while all those in the other village were free of mottling. McKay and Black also made the astute observation that towns in which mottled enamel was common most often derived their water supply from deep wells. Those villages relatively free of the abnormality usually obtained their water from rivers or streams. By 1916, it was clear that the disease was water-borne.[88] In 1925, McCollum and his associates demonstrated that the addition of small amounts of fluorine to the diets of growing rats caused the upper incisor teeth to overgrow and become curved so that they pierced the palate; lower incisors became eroded to the gum line.[86] The teeth in these rats became brittle, opaque, and white. Not until several years later, however, was fluorine identified by three separate groups of investigators as the constituent of drinking water which was responsible for mottling in human subjects.[21, 48, 138] The designation "chronic dental fluorosis" was then given to the abnormality.

Chronic dental fluorosis has been recognized on every continent. Its distribution, as recorded by Dean, is given in Fig. 22.[48] The West Texas Panhandle region constitutes the largest known region of endemicity in the United States. Concentrations in drinking water of 1 ppm are apparently safe, but the incidence of the disease increases as the concentration in water becomes greater. At 2.5 ppm the incidence is 75 to 80 per cent, and at 6 ppm, all members of the population show the condition.[31, 35]

Fluorine acts during the period of calcification of the teeth, so that as the teeth erupt they show the characteristic changes. The teeth have dull chalky white patches distributed over the surface, and in some cases the whole tooth surface may present a dead-white unglazed appear-

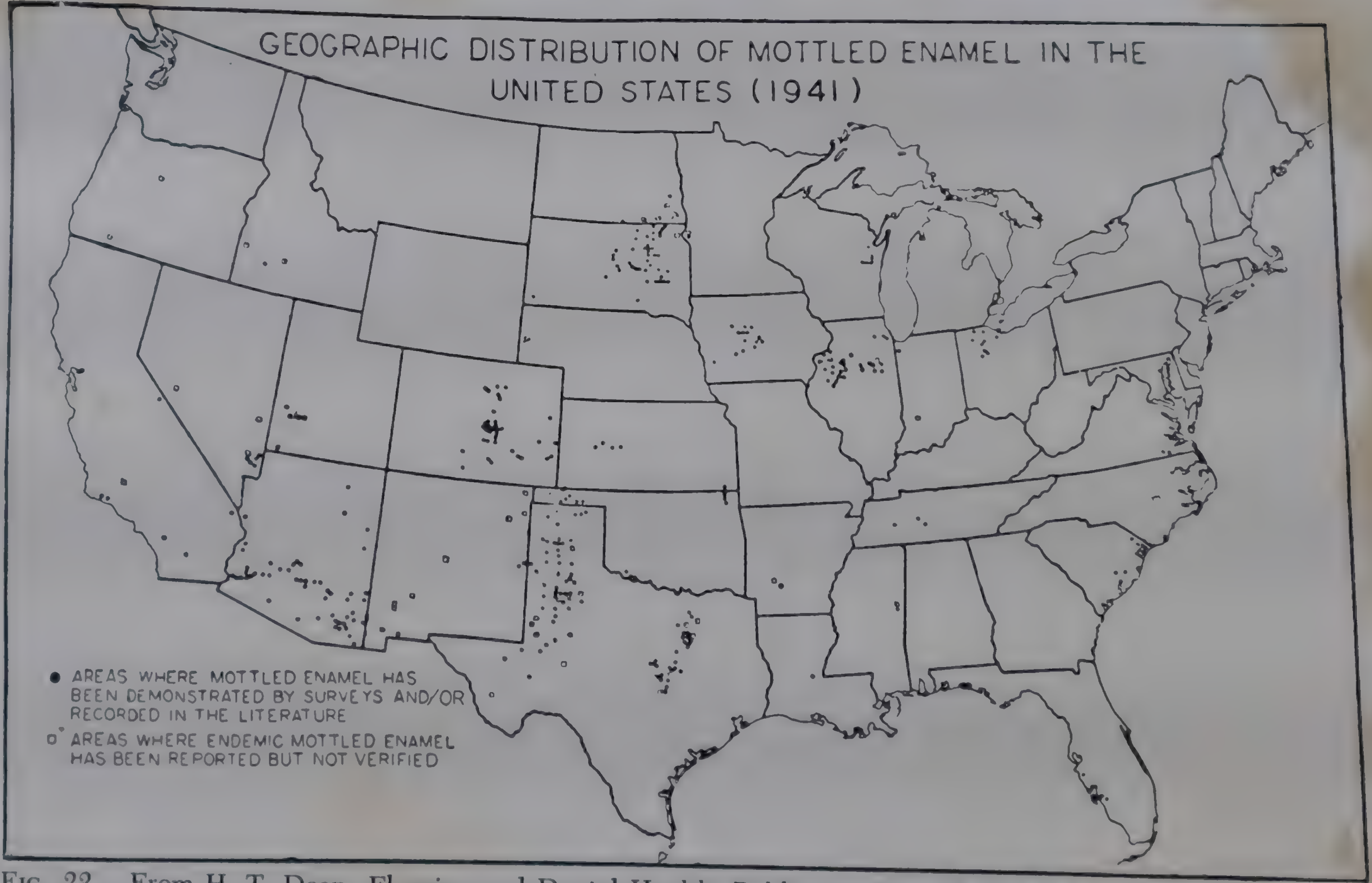
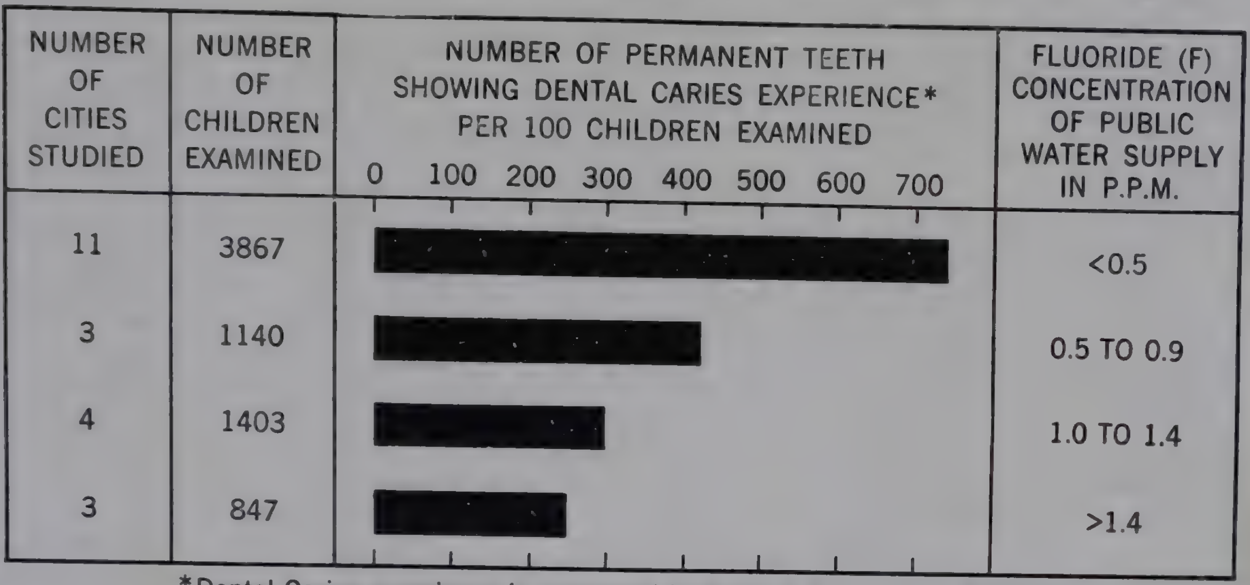

GEOGRAPHIC DISTRIBUTION OF MOTTLED ENAMEL IN THE UNITED STATES (1941)
● AREAS WHERE MOTTLED ENAMEL HAS BEEN DEMONSTRATED BY SURVEYS AND/OR RECORDED IN THE LITERATURE
○ AREAS WHERE ENDEMIC MOTTLED ENAMEL HAS BEEN REPORTED BUT NOT VERIFIED

FIG. 22. From H. T. Dean: Fluorine and Dental Health. Publication No. 19 of the American Association for the Advancement of Science, p. 9.

ance. There may be discrete or confluent pitting of the enamel. Sometimes the teeth take on a brown stain and look corroded. The disfigurement is permanent although dentists are now able to remove the stain.[48] (See VIII*f*, p. 85.) Hypoplasia of the enamel and dentin may be seen microscopically. There is a failure in the development of the cementing interprismatic substance of the enamel with incomplete calcification of the enamel rods and of the dentin. Pitting is caused by a breaking off of the end of the enamel prisms.[124]

2. RELATIONSHIP BETWEEN FLUORINE AND DENTAL CARIES

That the presence of fluorine in the diet decreases the incidence of dental caries is indicated by three types of evidence. In the first place, survey studies have demonstrated that the number of carious teeth per person is greater in communities which have a low-fluorine water supply than in those where the fluorine content is above 1 ppm (Fig. 23).[33] Furthermore, in those cities where the water supply has been changed to reduce the fluorine content from toxic levels, the incidence of caries is appreciably greater among children born since the water supply was changed than in those who had been exposed to the high fluorine intake.[32] Secondly, chemical analysis has shown that sound enamel from sound teeth contains more fluorine than that from carious teeth.[3] Lastly, in animal experiments, rats have been found to develop less caries on a



*Dental Caries experience is computed by totaling the number of filled teeth (past Dental Caries), the number of teeth with untreated Dental Caries, the number of teeth indicated for extraction, and the number of teeth missing (presumably because of Dental Caries).

FIG. 23. Amount of dental caries (permanent teeth) observed in 7257 selected 12-14 year old white school children of 21 cities of 4 states classified according to the fluoride concentration of the public water supply.

caries-producing diet when fluorine is added to their ration.[5] The mechanism by which fluorine exerts its caries-resistant properties is not known with certainty, but it appears to be by one or both of the following: (1) by modifying tooth structure so as to confer a degree of caries immunity by reducing the solubility of enamel in the acids associated with the caries process,[40] or (2) by inhibiting bacterial action (enzyme inhibition) on food particles and on the tooth. Rough correlations have been obtained between the fluorine content of drinking water and the *L. acidophilus* bacilli in the mouth.[34]

On the basis of this evidence, several studies have been designed to test the practicability of controlling dental caries en masse by fluorinating the communal water supply.[33, 147] The cities of Grand Rapids, Michigan; Newburgh, New York; Midland, Michigan; Brantford, Ontario; and Sheboygan, Wisconsin, have added to their fluorine-low water enough of the element to raise the concentration to 1 ppm, the level thought to be optimal for dental health. No technical difficulties have been encountered, and the cost of fluorination in Grand Rapids is only about seven cents per person per year. These trials are definitely regarded as experimental. Other data indicate that if the dental caries rate is favorably influenced at all, improvement will probably occur only in children who were under the age of eight before the change was made. It has not been shown that the use of fluoride waters or of an increased intake of fluorine from other sources is beneficial during the posteruptive life of a tooth.

Of related interest is the significant observation that the addition of approximately 40 ppm of fluorine to the diet of rats during pregnancy and lactation decreased caries in the offspring.[24] Furthermore, epidemiologic evidence indicates that dental caries may be reduced in children not directly exposed to fluoride themselves but born of mothers who had, for a long period of time, been consuming drinking water containing excessive amounts of fluorine (14 ppm).[33]

Use of tablets, mouthwashes, and dentifrices containing fluorine has been warned against,[37] but carefully controlled observations are currently being made on the effect of topically applied solutions of fluoride on the caries rate.[4, 9, 19, 76, 78] Usually, a 2 per cent aqueous solution of sodium fluoride is employed and it has been found that 4 to 8 applications should be made. In children the incidence of caries is roughly about 25 per cent lower in treated than in untreated teeth. Furthermore, in one study which included permanent teeth, carious to begin with,[78] the number of additional surfaces which became carious were fewer in the fluoride-treated teeth by factors of 12.4, 25.2, and 33.1 per cent respectively during each of the first three years. One failure to reduce dental caries with topical application has been reported.[4] This study, however, was done on young adult males rather than on children; the results suggest that the procedure may not be of value when applied to teeth which have been in the mouth for a long time. Data indicate that the fluorine content of the entire enamel of teeth treated with topical applications is not increased. Much work remains to be done before final evaluation of the technic can be made or the most effective method of application be defined.

SOURCES AND METABOLISM OF FLUORINE

Fluorine is widely distributed in nature, particularly in areas rich in phosphates, aluminum, and volcanic ash. It is present in very small amounts in plant and animal tissues; data on its content in foods are now available.[85] Normal mixed diets usually provide 0.3 to 0.5 mg. fluorine per day. The content in cow's milk is only slightly affected by increasing the fluoride intake.[129] Water becomes contaminated with the element largely when it passes through rich mineral deposits.

Information about the metabolism or precise function of fluorine is extremely meager. Absorption depends in large part on the solubility of the fluorine-containing salt or material. Elimination occurs largely through the urine. Urinary excretion increases as the content of fluorine in drinking water increases, but with high levels of intake the kidney's efficiency in excreting the element probably diminishes.[35] Sweat and perhaps insensible perspiration also account for an appreciable loss of fluorine from the body. When quantities of fluorine up to 3–4 mg. are ingested daily, 90 per cent or more is eliminated in the urine and sweat. There seems, therefore, to be little danger that toxic amounts will be accumulated with water supplies providing up to about 1.9 ppm.

The highest concentrations of fluorine in the body occur in the skeleton and teeth. That fluorine modifies calcium and phosphorous metabolism is indicated by the fact that it decreases the severity of rickets in the rat but inhibits the healing process when fed together with vitamin D to rachitic animals.[124] The claim has also been made that fluorine has a synergistic action with thyroid in experimental animals and accentuates the effect produced by thyroid on the basal metabolic rate.[100]

EVIDENCES OF FLUORINE TOXICITY

In addition to chronic dental fluorosis, fluorine has been reported to cause certain skeletal abnormalities. Lesions resembling osteosclerosis have been reported in areas where inhabitants are exposed to large concentrations of fluorine for long periods of time.[62, 127] Young adults, however, subjected to the concentrations found in drinking water in this country show no effects on growth or incidence of bone fractures which can be attributed to the fluorine exposure.[85]

Domestic and experimental animals subjected to large intakes of fluorine may show degenerative and inflammatory renal changes. In India impaired renal function has been described in patients with a severe form of osteosclerotic change attributed to fluorine.[127] However, urinary findings in men living in the fluoride areas of the West Texas Panhandle, where the fluorine content of drinking water may be as high as 5–6 ppm, do not differ from the normal.[85]

Because fluorine is widely used in industry, insecticides, and sprays, acute poisoning is not unusual.[55] The fatal oral dosage is approximately 0.5 Gm. per Kg. of body weight. The following manifestations appear: salivation, nausea, vomiting, muscular weakness, excitement and tremors, and convulsions. The blood pressure falls because of central vasomotor depression and a direct toxic effect on the myocardium. After an initial acceleration and deepening of respiration, respiration is depressed and death occurs.

MANGANESE

Manganese deficiency has never been recognized in animals or man under natural conditions. Proof that the element is an essential nutrient has been obtained by the experimental production of deficiency in animals. Since manganese is widely distributed in plants and in animal tissues, the small amounts required for normal nutrition are easily assimilated from food.

Metabolism, Requirement, and Sources of Manganese

Manganese absorbed from the intestinal tract is transported to all tissues of the body. Its concentration in blood is approximately .002 mg. per 100 cc.; about twice as much is present in plasma as in cells.[126] The liver contains the largest amount, but relatively high concentrations are also found in the pancreas, kidneys, and adrenals.[54, 105] The thyroid is peculiar in that it normally contains relatively little manganese but has the capacity for storing the metal in amounts out of all proportion to that stored by the other organs.[103] There is a great rise in the percentage of manganese in the human fetal liver during the last months of pregnancy.[101] Manganese is excreted largely by the liver (bile) and by the colon.[54]

The exact functions of manganese are not known. It is: (1) a growth factor, (2) important in maintaining normal reproductive functions, (3) related at least indirectly to the metabolism of calcium and phosphorus, and (4) an activator of certain enzymes, particularly cozymase, carboxylase, cholesterinase, and phosphatase.[124] Manganese is a part of the molecular structure of the enzyme arginase, which is utilized in the formation of urea.[106] The liver of manganese-deficient rats exhibits a decrease in arginase activity; addition of the metal restores that activity to normal.[124] Since rats on a thiamine-deficient diet become more quickly depleted when excess manganese is given, the suggestion has been made that these two substances are metabolically related.[109] That manganese is essential to normal embryonic development has been shown for the rat and the chick embryos.[27, 81]

The human requirement for manganese is not known. From data obtained by balance studies, the suggestion has been made that the diet of small children should contain between 0.2 and 0.3 mg. per Kg. daily.[45] How closely this estimate approximates actual requirements is not known. The daily adult human diet contains approximately 4 mg.[74] Plant foodstuffs are the chief source of manganese in the diet; blueberries, the bran of cereals, and nuts are particularly rich sources.[99, 126] Milk contains small amounts; the transfer of radioactive manganese from the mother to the tissues of nursing rats has been traced.[54]

Manifestations of Manganese Deficiency

When mice and rats are reared on a manganese-deficient diet, growth is decreased, and abnormalities of reproductive functions develop. There are three distinct stages of manganese deficiency in the female.[124] In the least severe stages of manganese deficiency the deficient female gives birth to viable young which develop symptoms of ataxia and poor equilibrium. In the second stages, nonviable young are born. In the most severe depletion, the oestrus cycle is disturbed and sterility results.[13] Males born of mothers given a manganese-deficient diet during pregnancy are sterile and show testicular atrophy. However, male rats born of normal mothers and fed a deficient amount of manganese from the time of weaning have apparently normal testicular functions.

Pigs fed a diet containing only .0011 to .0014 per cent manganese develop lameness which can be prevented by manganese supplementation.[90] Manganese is needed together with choline and biotin to prevent a disease in fowl called perosis. Perosis is characterized grossly by an enlargement of the tibial-metatarsal joint, twisting and bending of the distal end of the tibia and of the proximal end of the metatarsus, and slipping of the gastrocnemius tendon from its condyle.[49] Eggs produced by manganese-deficient hens hatch very poorly; when the embryos do grow, they show chondrodystrophic changes.[81]

Several years ago it was thought that manganese as well as copper might be necessary for normal hemoglobin metabolism, but more recent studies have denied this claim.[43] Polycythemia produced by cobalt is not sustained unless manganese is present.[97] There is no known rationale for the regrettable practice of including manganese in various "shot gun" anti-anemic preparations used clinically.

Toxicity of Manganese

Because manganese is used in the manufacture of steel and of dry batteries, there is considerable industrial exposure to its dust or fumes. The metal is apparently absorbed through the lungs and produces toxic manifestations. These have been reviewed by v. Oettingen.[95] The clinical syndrome simulates a progressive hepatolenticular degeneration and in some respects resembles Parkinson's disease. The facial expression is masklike, the voice monotonous. An intention tremor is almost always present. Patients frequently have muscular pain, muscular rigidity, and a spastic gait. Tendon reflexes are exaggerated; ankle and patellar clonus are commonly found. Some patients also develop cirrhosis of the liver. There is no satisfactory therapy.

ZINC

The adult human body contains approximately 2.2 Gm. of zinc,[126] an amount considerably larger than that for the other trace elements. No manifestations of deficiency under natural conditions have been reported. The metal is widely distributed in foods and roughly from 12 to 20 mg. daily are contained in the normal human diet. Experimentally in rats and mice, zinc has been shown to be an essential element, in that deficiency brings about a disturbance of growth and alopecia.[29, 30, 50, 66, 134] The role of zinc in biologic processes is little understood, but its occurrence in several important enzymes indicates that it is concerned mainly with enzyme activity. A thorough review dealing with the biologic, hygienic, and medical properties of zinc was published in 1945.[60]

Metabolism, Human Requirements and Sources

The blood of animals and man contains about 0.5 to 1.0 mg. of zinc per 100 cc., the concentration in the white and red cells being approximately twice that in the plasma. Injected radioactive zinc in dogs and mice[121, 122] disappears rapidly from the plasma and is initially concentrated in the liver, which at the end of several hours contains almost 40 per cent of any injected dose. There is also a considerable accumulation of zinc in the pancreas, kidneys, and spleen. The metal is gradually lost from these organs and seems to become deposited more generally in other tissues. The rate of excretion does not entirely account for the amounts which disappear from the liver, pancreas, and kidneys; in its widely distributed form it remains in the body for long periods.

Valee and his co-workers have studied the content of injected radioactive zinc in the circulating blood cells of dogs and man.[137] The zinc content of canine leukocytes rises and falls in more or less regular cycles of from five to eight days. It is suggested that these cycles probably represent the life span of the leukocytes, reflecting a fairly constant rate of reutilization of zinc in the leukocyte cycle. The same workers also found subnormal values in the white cells in leukemia and increased levels in the erythrocytes in untreated pernicious anemia.[52] Their findings suggest that zinc plays an important role in the metabolism of tissue and blood cells and that the body has a mechanism for its conservation and reutilization.

It appears that the physiologic functions served by zinc are associated with the action of enzymes. Carbonic anhydrase, the enzyme which accelerates the reaction,

$$H_2CO_3 \rightleftarrows CO_2 + H_2O$$

is a zinc-protein complex.[75] All of the zinc in red blood cells is in the form of carbonic anhydrase. The metal has also been found in purified preparations of uricase[63, 141] and phosphatase.[22] In the presence of amino acids there is a marked activation of intestinal phosphatases by traces of zinc, although the metal has less effect on kidney and bone phosphatases.[68] These observations correlate well with the finding of low intestinal phosphatase activity in the zinc-deficient rat.

Zinc is present in some preparations of insulin,[114] and the addition of zinc salts to insulin causes a delay in the physiologic action of the latter with a prolongation of the hypoglycemic effect.[115] Furthermore, the zinc content of the pancreas of diabetic patients is only about one-half that of normal individuals;[116] even so, however, the amount remaining is more than would be required for the formation of zinc insulin. Whether or not zinc is essential to the synthesis or action of insulin is not yet known. Other hormone associations of zinc are these: (1) it augments the action of the follicle-stimulating and lutenizing hormones of the anterior pituitary when tested on hypophysectomized rats;[11] and (2) it prolongs the water retaining action of pituitrin in frogs.[12] What other functions the metal has, if any, are still to be determined.

The elimination of zinc is accomplished largely by the gastrointestinal tract, urinary excretion being comparatively small. McCance and Widdowson found that normal persons excreted about 0.3 mg. of zinc per day in the urine; this amount did not vary with the intake of the metal by mouth, nor was it appreciably raised by intravenous injection.[83] Patients with albuminuria excreted about seven times the normal amount of zinc in the urine. Fecal excretion by normal adults was roughly equivalent to the amount ingested. Some, but not all, of the subjects eliminated additional zinc by way of the bowel when amounts up to 6 mg. per day were injected intravenously for two weeks. Studies with radioactive zinc in mice and dogs[91, 121] have further demonstrated that the metal is excreted largely by the gastrointestinal tract and only slightly by the kidneys. A large proportion of injected Zn^{65} was eliminated by way of the external secretion of the pancreas and in the duodenal juice, but little appeared in the bile.

The human requirements for zinc have not been defined. Preschool children retain between 0.3 and 0.6 mg. of dietary zinc per Kg. of body weight per day,[118, 132] but it is not known how closely this approximates actual need. Eggleton observed a number of Chinese subjects, some of whom had beriberi, whose diets provided only about 6 mg. of zinc per day. Their blood levels of zinc were low and the concentration in epidermal structures (toenails, fingernails, and skin) was reduced to half the normal value. He suggested that "zinc deficiency may be a factor in the beriberi syndrome," but was not able to relate any specific clinical manifestations to a lack of zinc.[39, 40, 41] Dietary deprivation must apparently be even greater if zinc deficiency is to be precipitated. Fruits, vegetables, milk, and tissues contain from 2 to 5 mg. of the metal per 100 Gm.[39, 126] If zinc is an essential element for man, as it probably is, there is little danger that diets will be deficient unless they are extremely bizarre.

Zinc Deficiency

Rats and mice fed a diet containing 1.6 ppm or less of zinc gain weight poorly and develop an alopecia about the neck and shoulders which sometimes spreads and involves the whole ventral surface of the body.[29, 134] Microscopic studies of zinc-deficient animals have shown extreme parakeratosis with a thick layer of partially keratinized cells in the esophagus. The skin has shown hyperkeratinization, thickening of the epidermis, and loss of hair follicles with persistence of the sebaceous glands. In an occasional animal, vascularization of the cornea with leukocytic infiltration has been observed.[50] This latter change is similar to the ocular lesions of ariboflavinosis. Carbonic anhydrase activity is not decreased in zinc-deficient rats,[50, 67] and there seems to be no disturbance of carbohydrate metabolism, although the absorption of glucose is apparently impaired.[65] Instances of sterility in cattle have been attributed to zinc deficiency and are said to have been cured with zinc oxide.[92]

Toxicity of Zinc

In experimental animals the feeding of excess dietary zinc has been reported to produce hypochromic anemia, subnormal growth, and reproductive failure.[133] The metal was found to have two separate effects on rats: one upon the hemoglobin level, and the other upon the growth rate. Partial protection from the anemia could be obtained by the simultaneous administration of copper, liver extract, or a combination of copper with iron and cobalt. Liver extract also combated the growth inhibition due to zinc.[30]

The amounts of zinc present in food or water are not sufficient to cause toxic symptoms. However, enough zinc may apparently be dissolved from cooking utensils made of galvanized iron to cause poisoning if the food is acid in reaction. It is reported that a group of soldiers were accidentally poisoned by drinking limeade prepared in a galvanized can.[15] Nausea, vomiting, diarrhea, and abdominal pain are common symptoms. The inhalation of zinc dust results in a syndrome called "metal fume fever" in which chills, fever, and a marked leukocytosis occur. Zinc seems to exert its toxic action by precipitating the protein of the gastrointestinal mucosa or the bronchial epithelium.

BIBLIOGRAPHY

1. Ahmad, B., and McCollum, E. V. The cobalt content of some food materials from different parts of the United States. *Am. J. Hyg.* 29:24, Section A, 1939.
2. Albisten, H. E., Bull, L. B., Dick, A. T., and Keast, J. C. A preliminary note on the etiology of enzootic jaundice, toxemic jaundice, or "yellows" of sheep in Australia. *Australian Vet. J.* 16:233, 1940.
3. Armstrong, W. D., and Brekhus, P. J. Possible relationship between the fluorine content of enamel and resistance to dental caries. *J. Dent. Research* 17:393, 1938.
4. Arnold, F. A., Jr., Dean, H. T., and Singleton, D. E. The effect on caries incidence of a single topical application of a fluoride solution to

the teeth of young adult males of a military population. *J. Dental Research* 23:155, 1944.

5. Ast, D. B. The caries-fluorine hypothesis and a suggested study to test its application. *Pub. Health Rep.* 58:857, 1943.

6. Baxter, C. R. Copper and cobalt in anemia. *Brit. M. J.* 534, 1939.

7. Bennetts, H. W., and Beck, A. B. Enzootic ataxia and copper deficiency in western Australia. *Bull. Counc. Sci. Indust. Res. Australia* 147:52, 1942.

8. Bennetts, H. W., and Chapman, F. E. Copper deficiency in sheep in western Australia. *Australian Vet. J.* 13:138, 1937.

8a. Berk, L., Burchenal, J. H., and Castle, W. B. Erythropoietic effect of cobalt in patients with or without anemia. *New England J. Med.* 240:754, 1949.

8b. Berk, L., Castle, W. B., Welch, A. D., Heinle, R. W., Anker, R., and Epstein, M. Observations on the etiologic relationship of achylia gastrica to pernicious anemia. X. Activity of vitamin B_{12} as food (extrinsic) factor. *New England J. Med.* 239:911, 1948.

8c. Berk, L, Denny-Brown, D., Finland, M., and Castle, W. B. Effectiveness of vitamin B_{12} in combined system disease, rapid regression of neurologic manifestations and absence of allergic reactions in a patient sensitive to injectable liver extracts. *New England J. Med.* 239:328, 1948.

8d. Bethell, F. H., Meyers, M. C., and Neligh, R. B. Vitamin B_{12} in pernicious anemia and puerperal macrocytic anemia. *J. Lab. & Clin. Med.* 33:1477, 1948.

9. Bibby, B. G. "Topical applications of fluorides as a method of combatting dental caries." In Dental Caries and Fluorine: *Publ. of the A.A.A.S.*, p. 93, 1946.

10. Bichel, J. Studies on erythrocytes' content of reduced glutathione, and its relation to hematopoiesis. *Acta. med. Scandinav.* 117:474, 1944.

11. Bischoff, F. Factors influencing the augmentation effects produced by zinc on copper when mixed with gonadotropic extracts. *Am. J. Physiol.* 121:765, 1938.

12. Boyd, E. M., and Clark, K. J. The prolongation by zinc salts of a water balance reaction of posterior hypophyseal extract. *Am. J. M. Sc.* 198:171, 1939.

13. Boyer, P. D., Shaw, J. J., and Phillips, P. H. Studies on manganese deficiency in the rat. *J. Biol. Chem.* 143:417, 1942.

14. Briskas, S., Lesné, E., and Polonovski, M., Cuivre et croissance ponderale chez le cobaye en avitaminose C. *Compt. rend. Soc. de biol.* 138:111, 1944.

14a. Burk, D., Hearon, J., Caroline, L., and Schade, A. L. Reversible complexes of cobalt, histidine and oxygen gas. *J. Biol. Chem.* 165:723. 1946.

15. Callender, G. R., and Gentzkow, C. J. Acute poisoning by zinc and antimony content of limeade prepared in galvanized iron can. *Mil. Surgeon* 80:67, 1937.

16. Campbell, A. M. G., Daniel, P., Porter, R. J., Russell, W. R., Smith, H. V., and Innes, J. R. M. Disease of the nervous system occurring among research workers on swayback in lambs. *Brain* 70:50, 1947.

17. Cartwright, G. E. Dietary factors concerned in erythropoiesis. *Blood* 2:256, 1947.

18. Cartwright, G. E., Jones, P. J., and Wintrobe, M. M. Method for determination of copper in blood serum. *J. Biol. Chem.* 160:593, 1945.

19. Cheyne, V. D. Human dental caries and topically applied fluorine: A preliminary report. *J. Am. Dent. A.* 29:804, 1942.

20. Chou, Tung-pi, and Adolph, W. H. Copper metabolism in man. *Biochem. J.* 29:476, 1935.

21. Churchill, H. V. Occurrence of fluorides in some waters of the United States. *Ind. and Eng. Chem.* 23:96, 1931.

22. Cloetens, R. Reversible cleavage of the second metal of alkaline phosphatase. *Biochem. Ztschr.* 308:37, 1941.

23. Copp, D. H., and Greenberg, D. M. Studies in mineral metabolism with the aid of artificial radioactive isotopes: VI., Cobalt. *Proc. Nat. Acad. Sc.* 27:153, 1941.

24. Cox, G. J. Matuschak, M. C., Dixon, S. J. Dodds, M. L., and Walker, W. E. Experimental dental caries: IV., Fluorine and its relation to dental caries. *J. Dent. Research* 18:481, 1939.

25. Cronin, E. Copper and cobalt in anemia. *Brit. M. J.* 643, 1939.

26. Cunningham, I. J. Some biochemical and physiological aspects of copper in animal nutrition. *Biochem. J.* 25:1267, 1931.

27. Daniels, A. L., and Everson, G. J. The relation of manganese to congenital debility. *J. Nutrition* 9:191, 1935.

28. Davidson, L. S. P. Discussion on the treatment of anemias. *Proc. Roy. Soc. Med.* 26:616, 1933.

29. Day, H. G. The effects of zinc deficiency in the mouse. *Federation Proc.* 1:188, 1942.

30. Day, H. G., and McCollum, E. V. Effects of acute dietary zinc deficiency in the rat. *Proc. Soc. Exper. Biol. & Med.* 45:282, 1940.

30a. Day, L. A., Hall, B. E., and Pease, G. L. Macrocytic anemia of pregnancy refractory to vitamin B_{12} therapy; response to treatment with folic acid: report of a case. Proc. Staff Meet., Mayo Clin. 24:149, 1949.

31. Dean, H. T. Chronic endemic dental fluorosis (mottled enamel). *J.A.M.A.* 107:1269, 1936.

32. Dean, H. T., Jay P., Arnold, F. A. Jr., and Elvove, E. Domestic water and dental caries. *Pub. Health Rep.* 56:365, 1941.

33. Dean, H. T. Fluorine and dental caries. *Am. J. Orthodontics* 33:49, 1947.

34. Dean, H. T., Jay, P., Arnold, F. A., Jr., McClure, E. J., and Elvove, E. Domestic water and dental caries, including certain epidemiological aspects of oral L. Acidophilus. *Pub. Health Rep.* 54:862, 1939.
35. DeEbs, F. Chronic fluorine intoxication. *Medicine* 12:1, 1933.
36. Eden, A., and Green, H. H. Micro-determination of copper in biological material. *Biochem. J.* 34:1202, 1940.
37. Editorial. *J. Am. Dent. A.* 34:345, 1947.
38. Eggleton, W. G. E. Trace elements in nutrition. *Caduceus* (Univ. of Hong Kong) 17:47, 1938.
39. Eggleton, W. G. E. The occurrence of zinc in foodstuffs and in the human body. *Caduceus* (Univ. of Hong-Kong) 17:103, 1938.
40. Eggleton, W. G. E. The zinc and copper content of the organs and tissues of Chinese subjects. *Biochem. J.* 34:991, 1940.
41. Eggleton, W. G. E. The zinc and copper content of blood in beriberi, in conditions associated with protein deficiency and in diabetes mellitus. *Chinese J. Physiol.* 15:33, 1940.
42. Elliott, K. A. C. On the catalysis of the oxidation of cysteine and thioglycollic acid by iron and copper. *Biochem. J.* 24:310, 1930.
43. Elvehjem, C. A. Biological significance of copper and its relation to iron metabolism. *Physical Rev.* 15:471, 1935.
44. Elvehjem, C. A., Siemers, A., and Mendenhall, D. R. Effect of iron and copper therapy on hemoglobin content of the blood of infants. *Am. J. Dis. Child* 50:28, 1935.
45. Everson, G. J., and Daniels, A. L. A study of manganese retentions in children. *J. Nutrition* 8:497, 1934.
46. Ferguson, W. S., Lewis, A. H., and Watson, S. J. The teart pastures of Somerset: I., The cause and cure of teartness. *J. Agri. Sc.* 33:44, 1943.
47. Filmer, J. F. Enzootic marasmus of cattle and sheep. Preliminary report having special reference to iron and liver therapy. *Australian Vet. J.* 9:163, 1933.
48. Fluorine and Dental Health. Pub. 19, Am. Association for the Advancement of Sci. Wash. D. C., 1942.
49. Follis, R. Pathologic effects produced by deficiency of single metallic and nonmetallic elements. *Arch. Path.* 34:451, 1942.
50. Follis, R. H., Jr., and Day, H. G. Histological studies of the tissues of rats fed a diet extremely low in zinc. *J. Nutrition* 22:223, 1941.
51. Fowler, W. M., and Barer, A. P. The effect of copper and iron on hemoglobin regeneration. *J. Lab. & Clin. Med.* 26:832, 1941.
52. Gibson, 2nd, J. G., Vallee, B. L., Fluharty, R. G., and Nelson, J. E. Studies of the zinc content of the leucocytes in myelogenous leukemia. St. Louis, Fourth Internat. Cancer Res. Congress., 1947, p. 104.
53. Goetsch, Tompkins, Anne, and Moore, C. V. Unpublished observations.
54. Greenburg, D. M., Copp, D. H., and Cuthbertson, D. H. Studies in mineral metabolism with the aid of artificial radioactive isotopes:

VII., The distribution and excretion, particularly by way of the bile, of iron, cobalt, and manganese. *J. Biol. Chem.* 147:749, 1943.

55. Greenwood, D. A. Fluoride intoxication. *Physiol. Rev.* 20:582, 1940.

56. Griffith, W. H., Pavcek, P. P., and Mulford, D. P. The relation of the sulfur amino acids to the toxicity of cobalt and nickel in the rat. *J. Nutrition* 23:603, 1942.

57. Gross, H., Sandberg, M., and Holly, O. M. Changes in copper and iron retention in chronic diseases accompanied by secondary anemia; changes in liver, spleen and stomach. *Am. J. M. Sc.* 204:201, 1942.

57a. Hall, B. E., and Campbell, D. C. Vitamin B_{12} therapy in pernicious anemia. I & II. Proc. Staff Meet., Mayo Clin. 23:584, & 591, 1948.

57b. Hall, B. E., Morgan, E. H., and Campbell, D. C. Oral administration of vitamin B_{12} in pernicious anemia: I. Presence of intrinsic factor in Berkefeld-filtered pooled human gastric juice: Preliminary report. Proc. Staff Meet., Mayo Clin. 24:99, 1949.

58. Harrow, B. Textbook of Biochemistry. Philadelphia, Saunders, 1946.

59. Hart, E. B., Steenboch, H., Elvehjem, C. A., and Waddell, J. Iron in nutrition: VII. Copper as a supplement to iron for hemoglobin building in the rat. *J. Biol. Chem.* 77:797, 1928.

60. Hegsted, D. M., Mckibben, J. M., and Drinker, C. K. The biological, hygienic and medical properties of zinc and zinc compounds. *Pub. Health Rep.* Suppl. 179, 1945.

61. Henderson, L. M., McIntire, J. M., Waisman, H. A., and Elvehjem, C. A. Pantothenic acid in the nutrition of the rat. *J. Nutrition* 23:47, 1942.

62. Hodges, P. C., Fareed, O. J., Ruggy, G., Chudnoff, J. C. Skeletal sclerosis in chronic sodium fluoride poisoning. *J.A.M.A.* 117:1938, 1941.

63. Holmberg, G. G. Uricase purification and properties. *Biochem. J.* 33:1901, 1939.

64. Houk, A. E. H., Thomas, A. W., and Sherman, H. C. Some interrelationships of dietary iron, copper, and cobalt in metabolism. *J. Nutrition* 31:609, 1946.

65. Hove, E., Elvehjem, C. A., and Hart, E. B. The physiology of zinc in the nutrition of the rat. *American J. Physiol.* 119:768, 1937.

66. Hove, E., Elvehjem, C. A., and Hart, E. B. The physiology of zinc in the nutrition of the rat: Further studies on zinc deficiencies in rats. *Am. J. Physiol.* 124:750, 1938.

67. Hove, E., Elvehjem, C. A., and Hart, E. B. The relation of zinc to carbonic anhydrase. *J. Biol. Chem.* 136:425, 1940.

68. Hove, E., Elvehjem, C. A., and Hart, E. B. The effect of zinc on alkaline phosphatases. *J. Biol. Chem.* 134:425, 1940.

69. Hutchinson, J. H. The role of copper in iron deficiency: Anemia in infancy. *Quart. J. Med.* 7:397, 1938.

70. Innes, J. R. M. Swayback: Demyelinating disease of lambs with affinities to Schilder's encephalitis, and its prevention by copper. *J. Neurol. & Psychiat.* 2:323, 1939.

71. Innes, J. R. M., and Shearer, G. D. Swayback: Demyelinating disease of lambs with affinities to Schilder's disease in man. *J. Comp. Path.* 53:1, 1940.

72. Josephs, H. W. Treatment of anemia of infancy with iron and copper. *Bull. Johns Hopkins Hosp.* 49:246, 1931.

73. Kato, K. Iron-cobalt treatment of physiologic and nutritional anemia in infants. *J. Pediat.* 11:385, 1937.

74. Kehoe, R. A., Cholak, J., and Story, A. V. Spectrochemical study of the normal ranges of concentration of certain trace metals in biologic materials. *J. Nutrition* 19:579, 1940; Manganese, lead, tin, aluminum, copper, and silver in normal biological material. *J. Nutrition* 20:85, 1940.

75. Keilin, D., and Mann, T. Carbonic anhydrase. *Nature* 144:442, 1939.

76. Klein, H. The family and disease: V., Caries experience among parents and offspring exposed to drinking water containing fluoride. *Pub. Health Rep.* 62:1247, 1947.

77. Kleinberg, W., Gordon, A. S. and Charipper, H. A. Effect of cobalt on erythropoiesis in anemic rabbits. *Proc. Soc. Exper. Biol. & Med.* 42:119, 1939.

78. Knutson, J. W., and Armstrong, W. D. The effect of topically applied sodium fluoride on dental caries experience. *Pub. Health Rep.* 61:1683, 1947.

78a. Le Goff, G. M. Cobalt as vasodilator. *J. Pharmacol. & Exper. Therap.* 38:1, 1930.

79. Lesné, E., Polonovski, M., and Briskas, S. Role du cuivre dans l'utilisation de l'acide ascorbique par le cobaye. *Compt. rend. Acad. d. sc.* 217:406, 1943. (*Chem. Abstr.* 38:6339, 1944.)

80. Lottrup, M. C. Treatment of anemia in children with ferric and ferrous compounds, reduced iron and cupric sulfate. *Am. J. Dis. Child.* 47:1, 1934.

80a. Luhby, A. L., and Doan, C. A. Personal communication.

81. Lyons, M., and Insko, W. M. Jr. Chondrodystrophy in the chick embryo produced by a mineral deficiency in the diet of the hen. *Poultry Sc.* 16:365, 1937.

82. Maass, A. R., Michaud, L., Spector, H., Elvehjem, C. A., and Hart, E. B. Relationship of copper to hematopoiesis in experimental hemorrhagic anemia. *Am. J. Physiol.* 141:322, 1944.

83. McCance, R. A., and Widdowson, E. M. Absorption and excretion of zinc. *Biochem. J.* 36:692, 1942.

84. McCance, R. A., and Widdowson, E. M. Mineral metabolism. *Am. Rev. Biochem.* 13:315, 1945.

85. McClure, F. J. "Nondental physiological effects of trace quantities of fluorine." In Dental Caries and Fluorine: *Publ. of the A.A.A.S.* p. 74., 1946.

86. McCollum, E. V., Simmons, N., Becker, J. E., and Bunting, R. W. The effect of additions of fluorine to the diet of the rat on the quality of the teeth. *J. Biol. Chem.* 63:533, 1935.

87. Mackay, H. M. M. Copper in the treatment of nutritional anemia in infancy. *Arch. Dis. Childhood* 8:145, 1933.

88. McKay, F. S. in collaboration with Black, G. V. An investigation of mottled teeth. *Dental Cosmos* 58:477, 1916.

89. Maynard, L. A., and Loosli, J. D. Mineral nutrition. *Ann. Rev. Biochem.* 12:251, 1943.

90. Miller, R. C., Keith, T. B., McCarty, M. A., and Thorp, W. T. S. Manganese as a possible factor influencing the occurrence of lameness in pigs. *Proc. Soc. Exper. Biol. & Med.* 45:50, 1940.

91. Montgomery, M. L., Sheline, G. E., and Chaikoff, I. L. The elimination of administered zinc in pancreatic juice, duodenal juice, and bile of the dog as measured by its radioactive isotope (Zn^{65}). *J. Exper. Med.* 78:151, 1943.

92. Mussill, J. Zinc deficiency as cause of cattle sterility. *Wien tierärztl. Monatschr.* 28:136, 1941. (*Chem. Abstr.* 6609, 1942.)

93. National Research Council, Reprint and Circular Series, No. 115, Washington, D. C., Jan., 1943.

94. Neal, W. M., and Ahmann, C. F. The essentiality of cobalt in bovine nutrition. *J. Dairy Sc.* 20:741, 1937.

95. v. Oettingen. Manganese: Its distribution, pharmacology, and health hazards. *Physiol. Rev.* 15:175, 1935.

96. Orten, J. M., Underhill, F. A., Mugrage, E. R., and Lewis, R. C. Blood volume studies in cobalt polycythemia. *J. Biol. Chem.* 99:457, 1933.

97. Orten, J. M., Underhill, F. M., Mugrage, E. R., and Lewis, R. C. The effect of manganese on cobalt polycythemia. *J. Biol. Chem.* 99:465, 1933.

97a. Ott, W. H., Rickes, E. L., and Wood, T. R. Activity of crystalline B_{12} for chick growth. *J. Biol. Chem.* 174:1047, 1948.

98. Parsons, L. G., and Hawksley, J. C. The anhaematopoietic anaemias (deficiency diseases of erythron); nutritional anaemia, and the anaemias of prematurity, scurvy and coeliac disease. *Arch. Dis. Childhood* 8:117, 1933.

99. Peterson, W. H., and Skinner, J. T. Distribution of manganese in foods. *J. Nutrition* 4:419, 1931.

100. Phillips, P. H., English, H. E., and Hart, E. B. The influence of sodium fluoride on the basal metabolism of the rat under several experimental conditions. *Am. J. Physiol.* 113:441, 1935.

101. Rainage, H., Sheldon, J. H., and Sheldon, W., A spectrographic investigation of the metallic content of the liver in childhood. *Proc. Roy. Soc. Med.* 113:308, 1933.

02. Van Ravesteyn, A. H. Metabolism of copper in man. *Acta. med. Scandinav.* 118:163, 1944.

103. Ray, T. W., and Deysack, L. J. Storage of manganese by thyroid. Effect on oxygen consumption by guinea pigs. *Proc. Soc. Exper. Biol. & Med.* 51:228, 1942.

104. Redfield, A. C., Coolidge, T., and Montgomery, H. The respiratory proteins of the blood: II., The combining ratio of oxygen and copper in some bloods containing hemocyanin. *J. Biol. Chem.* 76-197, 1928.

105. Reiman, C. K., and Minot, A. S. A method for manganese quantitation in biological material together with data on the manganese content of human blood and tissues. *J. Biol. Chem.* 42:329, 1929.

106. Richards, M. M., and Hellerman, L. Activation of enzymes: VI., Purified liver arginase: Reversible inactivation and reactivation. *J. Biol. Chem.* 134:237, 1940.

106a.Rickes, E. L., Brink, N. G. Koniuszy, F. R., Wood, T. R., Folkers, K. Vitamin B_{12} as cobalt complex. *Science* 108:134, 1948.

106b. Robinson, J. C., James, G. W. III, and Kark, R. M. The effect of oral therapy with cobaltous chloride on the blood of patients suffering with chronic suppurative infection. *New England J. Med.* 240:749, 1949.

107. Sachs, A., Levine, V. E., and Fabian, A. A. Copper and iron in human blood: I., Normal men and women. II., Blood copper and iron in men and women with various pathologic conditions. *Arch. Int. Med.* 55: 227, 241, 1935.

108. Sachs, A., Levine, V. E., Hill, F. C., and Hughes, R. Copper and iron in human blood. *Arch. Int. Med.* 71:489, 1943.

109. Sandberg, M., Perla, D., and Holly, O. M. Interdependence of vitamin B_1 and manganese, iron, and copper metabolism in B_1 deficient rats. *Proc. Soc. Exper. Biol. & Med.* 42:368, 1939.

110. Schultze, M. O. Metallic elements and blood formation. *Physiol. Rev.* 20:37, 1940.

111. Schultze, M. O. Relation of copper of cytochrome oxidase and hematopoietic activity of bone marrow of rats. *J. Biol. Chem.* 138:219, 1941.

112. Schultze, M. O., and Kiuken, K. A. The effect of deficiencies in copper and iron on the catalase activity of rat tissues. *J. Biol. Chem.* 137:727, 1941.

113. Schultze, M. O., and Simmons, S. J. The use of radioactive copper in studies on nutritional anemia of rats. *J. Biol. Chem.* 142:97, 1942.

114. Scott, D. A. Crystalline insulin. *Biochem. J.* 28:1592, 1934.

115. Scott, D. A., and Fisher, A. M. The effect of zinc salts on the action of insulin. *J. Pharmacol. & Exper. Ther.* 55:206, 1935.

116. Scott, D. A., and Fisher, A. M. The insulin and the zinc content of normal and diabetic pancreas. *J. Clin. Investigation* 17:725, 1938.

117. Scoular, F. I. Quantitative study, by means of spectographic analysis of copper in nutrition. *J. Nutrition* 16:437, 1938.

118. Scoular, F. I. A quantitative study, by means of spectrographic analysis of zinc in nutrition. *J. Nutrition* 17:103, 1939.

119. Sedgwick, E., Smith, M. M., and Ellis, G. H. The blood picture of iron and copper deficiency anemias in the rabbit. *Am. J. Physiol.* 142: 179, 1944.

120. Segard, C. P. Our present knowledge of the action and sources of copper in nutrition anemia. *Am. J. Digest. Dis.* 6:315, 1939.

121. Sheline, G. E., Chaikoff, I. L., Jones, H. B., and Montgomery, M. L. Studies on the metabolism of zinc with the aid of its radioactive isotope: I., The excretion of administered zinc in urine and feces. *J. Biol. Chem.* 147:409, 1943.

122. Sheline, G. E., Chaikoff, I. L., Jones, H. B., and Montgomery, M. L. Studies on the metabolism of zinc with the aid of its radioactive isotope: II., The distribution of administered radioactive zinc in the Tissues of mice and dogs. *J. Biol. Chem.* 149:139, 1943.

123. Sheline, G. E., Chaikoff, I. L., and Montgomery, M. L. The elimination of administered cobalt in pancreatic juice and bile of the dog, as measured with radioactive isotopes. *Am. J. Physiol.* 145:285, 1946.

124. Shils, M. E., and McCollum, E. V. The trace elements in nutrition. *J.A.M.A.* 120:609, 1942.

125. Shils, M. E., and McCollum, E. V. Further studies on the symptoms of manganese deficiency in the rat and mouse. *J. Nutrition* 26:1, 1943.

126. Shohl, A. T. Mineral Metabolism. New York, Reinhold, 1939, Chap. 11.

127. Shortt, H. E., McRobert, G. R., and Barnard, T. W. Endemic fluorosis in the Madras presidency. *Indian J. M. Research* 25:553, 1937-38.

127a. Smith, E. L. Purification of anti-pernicious anemia factors from liver. *Nature* 161:638, 1948.

127b. Smith, E. L. Presence of cobalt in the anti-pernicious anemia factor. *Nature* 162:144, 1948.

128. Smith, M. C., Lantz, E. M., and Smith, H. V. The cause of mottled enamel, a defect of human teeth. *Tech. Bull.* 32, Univ. Arizona Agric. Exp. Station. p. 253, 1931.

129. Smith, M. C., Vavick, M., and Smith, H. V. Fluorine content of milk as affected by the amount of fluorine in the drinking water of the cow. *J. Dent. Research* 20:286,1941.

130. Smith, S. E., and Larson, E. J. Zinc toxicity in rats: Antagonistic effects of copper and zinc. *J. Biol. Chem.* 163:29, 1946.

130a. Spies, T. D., Suarez, R. M., Lopez, G. G., Milanes, F., Stone, R. E., Toca, R. L., Arambura, T., and Kartus, S. Vitamin B_{12} as a therapeutic agent. *J.A.M.A.* 139:521, 1949.

131. Stanley, A. J., Hopps, H. C., and Schideler, A. M. Cobalt polycythemia: II., Relative effects of oral and subcutaneous administration of cobaltous chloride. *Proc. Soc. Exper. Biol. & Med.* 66:19, 1947.

132. Stern, A., Nalder, M., and Macy, I. G. Zinc retention in childhood. *J. Nutrition* 21:8, Suppl. 1941.

133. Sutton, W. R., and Nelson, V. E. Growth, reproduction, and blood changes produced in rats by means of zinc carbonate. *Proc. Iowa Acad. Sc.* 44:117, 1937.

134. Todd, W. R., Elvehjem, C. A., and Hart, E. B. Zinc in the nutrition of the rat. *Am. J. Physiol.* 107:146, 1934.

135. Tompsett, S. L. Copper content of blood. *Biochem. J.* 28:1544, 1934.

136. Underwood, E. F. The significance of the "trace elements" in nutrition. *Nutrition Abstr. and Rev.* 9:515, 1940.

137. Vallee, B. L., Fluharty, R. G. and Gibson, J. G., 2nd. Distribution of zinc in normal blood and organs studied by means of Zn^{65}. St. Louis, Fourth Internat. Cancer Res. Congress., 1947, p. 137.

138. Velu, H. Dystrophie dentaire des mammiféres des zones phosphatées (darmous) et fluorose chronique. *Comp. rend. Soc. de biol.* 108:750, 1931.

139. Voegtlin, C., Johnson, J. M., and Rosenthal, S. M. Catalytic action of copper in oxidation of crystalline glutathione. *Pub. Health Rep.* 46:2234, 1931.

140. Volker, J. F. Effect of fluorine on solubility of enamel and dentin. *Proc. Soc. Exper. Biol. & Med.* 42:725, 1939.

141. Wachtel, L. W., Hove, E., Elvehjem, C. A., and Hart, E. B. Blood uric acid and liver uricase of zinc deficient rats and various diets. *J. Biol. Chem.* 138:361, 1941.

142. Waltner, K. Therapeutische Versuche mit Kobalt. *Acta paediat.* 11:438, 1930.

143. Warren, C. O., Shubmehl, Q. D., and Wood, I. R. Studies on the mechanism of cobalt polycythemia. *Am. J. Physiol.* 142:173, 1944.

143a. Weissbecker, L., and Maurer, R. Kobaltwirkungen am Menschen. *Klin. Wchnschr.* 24-25:855, 1947.

144. Weissberger, A., and Luvalle, J. E. The autoxidation of ascorbic acid in the presence of copper. *J. Am. Chem. Soc.* 66:700, 1944.

144a. West, R. Activity of vitamin B_{12} in Addisonian pernicious anemia. *Science* 107:398, 1948.

144b. West, R., and Reisner, E. H. Jr. Treatment of pernicious anemia with crystalline vitamin B_{12}. *Am. J. Med.* 6:643, 1949.

145. Wintrobe, M. M. Clinical hematology. Philadelphia, Lea, 1946.

146. Wintrobe, M. M., Grinstein, M., Dubash, J. J., Humphreys, S. R., Ashenbrucker, H., Worth, W.: The anemia of infection: VI., The influence of cobalt on the anemia associated with inflammation. *Blood* 2:323, 1947.

147. Wolman, A. "Fluorine and the public water supply." In Dental Caries and Fluorine: *Publ. of the A.A.A.S.* p. 108, 1946.

148. Yoshikawa, H., Hahn, P. F., and Bale, W. F. Red cell and plasma radioactive copper in normal and anemic dogs. *J. Exper. Med.* 75:489, 1942.

Chapter 15

VITAMIN A MALNUTRITION

S. W. Clausen

Soon after the word *Vitamine* was coined by Funk,[22] it became apparent that food accessories were not all "amines"; nor were they all water-soluble. The observations of Osborne and Mendel[40] and of McCollum and Davis[36] showed that fat-soluble food accessories existed in milk and in cod liver oil. It was further shown that cod liver oil would prevent and cure rickets and would cure a disease of the eye known as xerophthalmia. These effects were ascribed to a single "fat-soluble vitamin A." C. E. Bloch[5-7] then showed by clinical reasoning that two different agencies were involved in the cure of these two disorders. He was able to cure rickets—without curing xerophthalmia—by exposing affected children to sunlight, and to cure xerophthalmia by the feeding of cod liver oil or vegetables. Final proof that cod liver oil contains two fat-soluble vitamins was brought by E. V. McCollum:[37] if a stream of air is passed through heated cod liver oil, the oil loses its ability to cure xerophthalmia without losing its ability to cure rickets. The same *vitamin A* has been reserved for the antixerophthalmic vitamin.

Vitamin A may be defined as a constituent of the diet of man and of animals, needed to maintain the structure and function of certain of the specialized epithelial and glandular tissues, the visual functions of the retina, and the growth of the body. In the absence of vitamin A, the epithelia of the conjunctiva, the respiratory tract, and the urinary tract lose their characteristic form and are replaced by keratinized epithelia; the epithelia of the lacrimal glands, the mucous glands of the respiratory tract, the sweat glands, and the sebaceous glands undergo a similar metaplasia. Unless secondary destructive changes (due often to infection) occur, complete recovery takes place when vitamin A is administered.

CHEMICAL NATURE AND PROPERTIES

The chemical nature of vitamin A is now known. It is a highly unsaturated alcohol and is stored in the body as an ester. Neither the alcohol nor the ester exists in plants. However, the ultimate source of all vitamin A is to be found in plants. The precursors—the provitamins A—are certain carotinoid pigments of deep yellow color: alpha-, beta-, and gamma-carotene, and possibly others. These provitamins are converted in the body to vitamin A. The fact that vitamin A itself is almost colorless, whereas the carotenes are intensely colored, for a time caused confusion among investigators.

The various carotenes which can serve as provitamin A are abundant—together with chlorophyll—in green leaves, in certain storage tissues such as tubers (e. g., carrots), and in fruits. They all contain a beta-ionone ring and a chain of carbon atoms connected by conjugated double bonds. The more important forms of provitamin A are isomeric hydrocarbons with the formula $C_{40}H_{56}$ and contain no oxygen. Beta-carotene is one of the most common; it usually occurs together with one or both of its isomers and with oxygenated carotinoid pigments called xanthophylls. The latter pigments are not definitely known to possess any nutritive function in animals; they are said to prevent oxidative destruction of the carotenes in the intestine. All carotinoid pigments are destroyed by oxygen at high temperature and by the action of light. They may be lost from hay if it is improperly cured. The pigments are relatively stable to heat in the absence of oxygen but can be destroyed by long cooking in open metallic vessels.

The chemical structure of vitamin A was elucidated by Karrer and Morf;[30] it is an unsaturated alcohol with the formula $C_{20}H_{28}OH$ and contains a beta-ionone ring. The livers of some fresh-water fish contain an isomeric form of vitamin A, called vitamin A_2 with biologic and chemical properties very similar to those of the form called vitamin A_1 which occurs in cod liver oil. Vitamin A is found in the storing tissues of the liver almost wholly as an ester with a higher fatty acid (said to be stearic acid). In cod liver oil, less than 1 per cent of the vitamin A is present as the alcohol. The pure vitamin has been prepared in quantity by the process of molecular distillation, and many of its pure esters have been prepared. Recently, the synthesis of the vitamin has been announced.

As its chemical structure suggests, vitamin A, like the carotenes, is unstable to oxygen at high temperatures. The less highly purified preparations are often more stable than the pure preparations possibly because of the presence in the former of antioxidants such as the tocopherols. It has been shown that under certain conditions the presence of tocopherols prevents loss of vitamin A in the intestinal tract.

For many purposes, vitamin A may be determined with sufficient accuracy by the color reaction of Carr and Price,[13] using antimony trichloride. A correction must be made for any carotene present. Carotene and xanthophyll may be determined by their color.

DEFINITION OF UNITS

Before the chemical natures of carotene and of vitamin A were known, it was necessary to express their vitamin A activity in arbitrary biologic units. Because of the small weights of material concerned and in order to include every substance with vitamin A activity, it is still convenient to use such units in practice. One international unit of vitamin A activity is defined as the quantity which is required per day to promote growth in a white rat receiving an otherwise vitamin-A–free diet. The official standard is 0.6 microgram of a pure preparation of beta-carotene.

PHYSIOLOGY

THE CAROTENES

The carotenes, as they occur in foods, enter the intestine enclosed as crystals or amorphous solids within vegetable cells. The process of cooking, by weakening the walls of the vegetable cells, aids in promoting the absorption of the carotinoids. Little is known about the mechanism of absorption. Bile acids and fats must be present. The absorption is decreased by diarrhea, and particularly by the presence of mineral oil. Carotene has been found in the lymph of the thoracic duct after ingestion of carotene in patients with fistula of the thoracic duct.

Some of the ingested carotene is converted to vitamin A. The site of the conversion is assumed to be the liver, although there is some evidence that it may be the intestinal wall. The mechanism of the conversion is not known; it appears to involve oxidation of part of the carotene molecule. The conversion is decreased in animals by thyroidectomy. The excessive levels in the skin and the blood of cretins are decreased by administering thyroid preparations. Untreated severe diabetes is often accompanied by high levels of blood carotene, as is lipoid nephrosis.

The concentration of carotinoids in human blood depends upon the carotinoid content of the diet. In healthy persons consuming an ordinary diet, the serum concentration is found to be between 80 and 120 micrograms per 100 cc. (see page 125). When the level rises above about 250 micrograms, the skin assumes a yellow color (xanthosis cutis) liable to be mistaken for jaundice. The palms, soles, lobes of the ears, and nasolabial regions are stained, but not the sclerae or the mucous membranes. The color never has a greenish cast but often tends toward an orange tint. When xanthosis cutis is due to diet alone, the color fades in the course of a few days or weeks after the intake of carotinoids is decreased. Exact diagnosis can be made by quantitative estimation of the level of carotinoids in the serum or plasma. Occasionally, children with xanthosis cutis have poor appetites, possibly because of faulty diet. The condition in itself is harmless.

The yellow color of human fat is due chiefly to carotenes. Repeated analysis of all the tissues has indicated that as much as 12 per cent of the entire "vitamin A stores" of the body may exist as carotene. However, it is not known whether these stores can be utilized as vitamin A.

It is not certainly known whether carotene per se has a biologic function in animals, or must first be converted into vitamin A. Experiments of Friderichsen[20-21] and of Wald[49] appear to show that the administration of carotene may improve dark adaptation more rapidly than does administration of vitamin A.

Absorption of Vitamin A

When vitamin A ester is ingested in oily solutions, such as cod liver oil or concentrates, saponification by pancreatic lipase takes place in the duodenum and upper jejunum; the vitamin which is absorbed is mostly in the alcohol form, and most of the absorption takes place in the upper part of the small intestine.[15]

The vitamin is promptly re-esterified in the wall of the intestine and is carried as the ester in the lymph and blood to the storage depots of the body. When vitamin A ester is finely emulsified so that the diameter of the droplets lies between 0.5 and 10 microns, saponification is not a necessary condition for absorption. Persons who cannot secrete pancreatic lipase are unable to absorb vitamin A ester unless it is administered in fine emulsions; such persons can absorb vitamin A alcohol dissolved in oil, whether emulsified or not.

Adequate absorption of vitamin A also requires the presence of bile salts; poor absorption is observed in infectious hepatitis, cirrhosis of the liver, and congenital obstruction of the bile ducts.

The absorption of vitamin A also requires normal function and structure of the small intestine. Faulty absorption is observed in sprue, celiac disease, colitis, deficiency of vitamin B complex, infections both enteral and parenteral, giardiasis, and deficiency of vitamin A itself.

The presence of mineral oil interferes with the absorption of vitamin A, but to a considerably smaller degree than it does with the absorption of carotene.

Vitamin A ester and alcohol are absorbed from deposits injected under the skin or into the muscle.

STORAGE OF VITAMIN A

The liver contains about 90 per cent of the entire amount of vitamin A found in the body of man and of some other animals. The capacity for storage by the liver is so great that in some species, such as the rat, enough may be stored after a single massive dose to meet the requirements for the duration of life. Human livers may contain enough vitamin A to suffice for three months to a year or more. The calculations are based upon the assumptions that (1) the vitamin will be used efficiently, and (2) the stores will be available when needed. Experiments with animals show that excessive stores are lost at a daily rate greater than the supposed daily requirements, and that small stores are lost at a daily rate less than the daily requirement. Infection, poisonings (especially with liver poisons), and hyperthermia increase the rate of loss. Little is known about any mechanism which might prevent inefficient loss of vitamin A in the storage tissues or in other tissues, or about mechanism for liberation of the vitamin from its stores. In the fasting person or animal, all of the vitamin A of the blood exists as the free or alcohol form, whereas an extremely small proportion of the vitamin in the stores exists as the alcohol.

The fetal liver contains vitamin A. The total amount found in the liver at birth varies considerably and is smaller in premature infants than in the mature. The amount does not increase when the infant receives milk without supplements such as cod liver oil or vegetables, but after such supplements a marked increase occurs. It appears that neither human milk nor cow's milk provides enough vitamin A to increase the stores in the liver of normal infants. Since the stores at birth may be low, as in the case of premature infants, and since infections and gastrointestinal disorders may lower the stores, it is obviously good practice to introduce supplements of vitamin A into the diet of all infants soon after the age of 2 weeks.

VITAMIN A OF THE BLOOD

Practically all the vitamin A of the blood is found in the plasma. Except after the ingestion of large amounts of the vitamin, all of the plasma vitamin A exists in the alcohol form. An increase of plasma vitamin A occurs after the ingestion of large amounts of the vitamin, and the increase is entirely in the ester form. It is believed that the ester is on its way to the storage tissues, and that the alcohol vitamin A is on its way from the liver to the tissues where it is needed.

The concentration of vitamin A in the plasma of normal persons is on the average about 75 I.U. per 100 cc. (see page 125). During infections, a considerable decrease occurs, which is dependent upon the severity and the duration of the infection. In lobar pneumonia, plasma vitamin A may disappear entirely. Artificial hyperthermia also causes a decrease in the plasma vitamin A. Experiments with animals show that the decrease in plasma levels due to infection or to hyperthermia occurs regardless of the quantity of vitamin A in the liver. Measurements of visual adaptation to dim light, if carried out during infections, are likely to suggest a vitamin A deficiency, but the deficiency is not necessarily in the stores. After the febrile period of an infection, the plasma vitamin A rises, sometimes to a considerable degree.

In depletion tests with animals, the plasma vitamin A does not fall until the stores are nearly exhausted. Only then does the plasma level of vitamin A reflect the amount in storage (see Chapter 6).

Determination of the level of plasma vitamin A therefore does not afford an estimate of the amount present in the stores.

Vitamin A and the Retina

The rods of the retina are concerned with vision in dim light. This function depends upon the presence in the rods of a substance called visual purple (rhodopsin). In certain fresh-water fish, the function depends upon another pigment, porphyropsin. The fact that faulty vision in dim light was known to occur in persons consuming diets lacking milk fat led to studies which identified the specific lack as vitamin A. In a brilliant series of investigations, Wald[48] was able to show that visual purple actually contains a derivative of vitamin A, an aldehyde called retinene, combined with a protein; that under the influence of light visual purple breaks down into the two constituents; and that in the dark, these constituents recombine to form visual purple. It has also been shown that porphyropsin contains a protein and an aldehyde, retinene$_2$, related to vitamin A_2. These observations provide a rational explanation for nutritional night-blindness and a basis for its treatment.

The cones of the retina have to do with color vision and with vision in bright light. According to Hecht,[26] the cones contain a pigment, visual violet, which requires the presence of vitamin A for its regeneration.

Reports to the effect that color-blindness can be relieved by vitamin A have not been confirmed.

PATHOLOGY OF AVITAMINOSIS A

When deficiencies occur in nature, several dietary factors may be deficient. For this reason, it is not always possible to ascribe the observed pathologic changes to the deficiency of a single factor. In experimental deficiencies, conditions can be so arranged that pathologic changes due to a single deficiency can be induced, and the sequence of changes can be studied not only during the period of including them, but also during the period of recovery. In the case of vitamin A deficiency, the pathologic changes are very nearly alike in many animals: monkeys, cattle, swine, dogs, rabbits, guinea pigs, rats, mice, and fowls; and many of the conditions are similar to those which have been observed in man. The important pathologic changes as described by Wolbach and Bessey[50] (quoted in part) are:

Epithelial Metaplasia

Certain specialized epithelia atrophy; the basal cells proliferate and differentiate into stratified keratinizing epithelia, which, regardless of the site, become identical with those of the epidermis. Any local infections which occur are secondary to the anatomic and functional changes such as stasis, loss of secretions, and loss of cilia. During recovery, in spite of the common morphology, the epithelium of each region returns to its normal type and function. The stratum germinativum differentiates directly into the normal type, without necessarily undergoing cell division. The cells above the stratum germinativum degenerate.

Not all the specialized epithelia of the body undergo metaplasia. In general, metaplasia affects secreting and covering epithelia whose functional cells have not the power to divide; the renal tubules and the liver parenchyma which have this power are not affected, nor are the secreting cells of the gastrointestinal tract. In the rat, metaplasia begins in the epithelium of the respiratory tract, then affects that of the salivary glands, the urinary tract, the eyes, the para-ocular glands, and the pancreas. Desquamated epithelium may cause obstruction, with cyst formation, e. g., at the base of the tongue and in the lung; the cysts are liable to infection. Soft calcium-containing concretions form in the urinary tract about masses of desquamated epithelium. Urinary lithiasis in man is, however, usually not due to vitamin A deficiency.

INCISOR TEETH IN RODENTS

In vitamin A deficiency, the enamel organ atrophies. A similar change has been reported by Boyle[11] in a human infant with vitamin A deficiency.

GROWTH OF BONE

Growth of bone is retarded in young animals long before gain in weight is affected. Because the central nervous system continues to grow, the cranial cavity and spinal canal become overcrowded. According to Wolbach,[50] all of the nervous manifestations—paralysis, and degeneration of various tracts of the spinal cord—are due to this cause.

The effect of partial vitamin A deficiency of the mother upon the fetus has been studied by Hale[24] in swine. He found anophthalmos and cleft palate. Warkany has reported the production of congenital defects of the eyes and of the heart of fetal rats.

Blackfan and Wolbach,[4] and Sweet and K'ang[45] have reported the pathologic findings in human cases of vitamin A deficiency; metaplasia of epithelium was in all respects like that in experimental animals.

HYPERVITAMINOSIS A

The administration of large amounts of vitamin A (40,000 I. U. per day) to growing rats causes loss of weight, soreness of the eyes, atrophy of the skin and loss of hair, decalcification and spontaneous fracture of bones, and hemorrhage. These symptoms, first induced by concentrates of fish-liver oils, are also caused by crystalline vitamin A acetate. They are accompanied by decrease in plasma prothrombin and by disappearance of the ascorbic acid of the tissues. It is claimed that administration of vitamin K or of ascorbic acid prevents them.

A single human case of possible hypervitaminosis A has been reported.[46]

The amounts of vitamin A needed to produce hypervitaminosis A in rats are approximately 10,000 times the requirement. The margin of safety is large. It is not definitely known whether any symptoms might occur when human beings receive moderate excesses of vitamin A, but the claim has been made that the menses of young women have been suppressed by such doses.

VITAMIN A REQUIREMENTS

The minimal daily requirement of vitamin A, refined as the quantity which will just suffice to relieve night blindness but not to produce significant storage, is remarkably uniform in many animals on the basis of their body weight. Guilbert[23] and his co-workers found that cattle, sheep, swine, horses, and rats have daily minimal requirements per kilogram of about 20 I.U. of vitamin A and 40 I.U. of carotene. Lewis and Haig,[34] testing infants for visual adaptation to dim light, found that their minimum requirement of vitamin A was 25 I.U. per Kg. per day. Booher and co-workers,[9-10] using a similar method, found that the daily requirement of adults was 25 to 50 I.U. of vitamin A as cod liver oil, and 50 to 74 I.U. as carotene. Batchelder and Ebbs[3] found that adults may need, as minimum, 74 to 84 I.U. per Kg. per day. Pregnancy and lactation increase the requirements. In the average diet of adults, carotene provides 60 to 80 per cent of the total vitamin A. Allowance must be made for individual variation in requirements and for storage. Taking such facts into consideration, the Food and Nutrition Board of the National Research Council has recommended 5000 I.U. as the daily allowance for adults. The daily allowances for various categories are given in Table A of the Appendix. These allowances are readily met by diets containing desirable amounts of green vegetables and dairy products. Appendix Table C, shows the contribution of average servings of selected foods.

Colostrum owes its color to carotene and is much richer in vitamin A than is milk. Summer milk may contain twice as much vitamin A as does winter milk; human milk often is richer than cow's milk. The vitamin A content of any milk depends upon the diet of the mother. The quantity of vitamin A provided by formulas for infants is less than the requirement for storage. Supplements of vitamin A (fish liver oils or carotene) are therefore indicated at least until the infant begins to get vegetables.

VITAMIN A DEFICIENCY IN MAN

Vitamin A deficiency is called "primary" when the diet is deficient. It is called "secondary" or "conditioned" (1) when there is a disorder which interferes with the absorption or storage of vitamin A, (2) when there is a disorder which interferes with the conversion of carotene to vitamin A, and (3) when rapid loss of vitamin A occurs in the body. The conditioned deficiencies of the first type have been observed in the celiac syndrome, sprue, cystic fibrosis of the pancreas, ulcerative colitis, operations upon the pancreas, operations which by-pass the duodenum, congenital partial obstructions of the jejunum, giardiasis, obstructions of the bile ducts, and cirrhosis of the liver. Conditioned deficiencies of the second type have been observed in diabetes mellitus and in hypothyroidism. Conditioned deficiencies of the third type are observed during infections such as pneumonia and scarlet fever, and even in mild respiratory infections in children. The plasma vitamin A may become undetectable, and visual adaptation to dim light may become impaired. These facts do not necessarily indicate exhaustion of stores. Obviously, the results of tests for dark adaptation must always be interpreted with caution when the characteristic anatomic changes of vitamin A deficiency are absent.

Primary vitamin A deficiency is uncommon in the United States, if one relies for diagnosis upon cardinal signs (night blindness as a complaint, xerophthalmia, and typical lesions of the skin). Dietary surveys, however, indicate that perhaps three-quarters of the population are not receiving the recommended amounts of vitamin A. Owing to the lack of any definition of suboptimal health, to the failure to improve health by the administration of vitamins to apparently healthy persons, and to the nonspecific character of the early signs and symptoms of any deficiency, it is difficult to support the view that vitamin A deficiency is common in the United States. More observations correlating diet and objective tests are needed, such as those of Frandsen[16] in Denmark, who found that persons subsisting on diets low in vitamin A regularly had lowered visual distinction which was improved by administration of the vitamin.

The specific manifestations of vitamin A deficiency in man are: Night blindness, xerophthalmia, and a characteristic dermatosis.

Manifestations of vitamin A deficiencies which are nonspecific, in the sense that they may be due to many other causes, are retardation of growth and lowered resistance to infection.

NIGHT BLINDNESS

Inability to see in dim light, accompanied by ability to see in bright light, is called night blindness. Night blindness is termed "hemeralopia," whereas inability to see in bright light with ability to see in dim light is termed "nyctalopia." According to their derivation, these words should mean exactly the opposite; however, the ancients used each word in both senses, and both words are now sometimes used for night blindness.

Hemeralopia may be due to organic disease of the retina, and slightly impaired ability to see in dim light may be a fixed characteristic of an individual. In general, however, acquired *curable* hemeralopia is due to deficiency of vitamin A, and it is the earliest manifestation of that deficiency. Its presence may be overlooked in a child, and in any person if its onset is gradual and its course continuous.

Night blindness may be epidemic when many persons at one time receive deficient diets. Its occurrence has been reported in Negro slaves in Brazil and in Chinese soldiers. The diet of the latter was rice, wheat, millet, very little flour, meat once a month, and no green vegetables at all. Aykroyd[2] found it to be common among Newfoundland fishermen and could relieve it in twelve to twenty-four hours with cod liver oil. It was common during the First World War among Austrian prisoners in Russia;[47] Austrian physicians (who were also prisoners) observed it among Russian peasants in the period of religious fasts before Easter. During this period all animal food, fish, eggs, milk, and butter, was forbidden; the diet was strictly vegetarian. Lightly cooked liver or cod liver oil were the popular remedies; the latter cured the night blindness in two or three days. Slight degrees of hemeralopia have been revealed by suitable technic by Danish investigators; Frandsen,[16] for example, found it in studying inmates of almshouses where the diet was deficient. Conditional night blindness is occasionally reported in persons whose diet is adequate in vitamin A but who are unable to absorb it. Nutritional night blindness is rare in the United States.

The person with hemeralopia may complain of his inability to see in the evening twilight, whereas he has less difficulty in the early morning twilight. His symptom may first be noticed after exposure to brilliant illumination. He may get some relief by wearing tinted glasses in the daytime. Street lamps may appear dim and amber colored. Coming from bright light into dim light, as in the theatre, he may be unable to find his way about for five minutes or more. In dim light he is liable to bump into other persons or objects and to stumble over obstacles. He may have difficulty in driving a car. The symptoms may vary in degree from time to time.

The diagnosis of nutritional hemeralopia depends upon proper appraisal of the diet and of any conditioning factors if the diet is adequate, and upon *rapid* improvement when vitamin A is administered. The presence of other signs of vitamin A deficiency is not necessary. Organic disease of the retina must be excluded. If response to adequate treatment with vitamin A does not occur within a few days, the diagnosis is unlikely.

Xerophthalmia and Keratomalacia

Dryness of the cornea and of the conjunctivas—xerophthalmia—has long been recognized in association with malnutrition. It is a manifestation of severe deficiency of vitamin A. Mori[40] gave an accurate clinical and histologic description of it as *hikan* in Japanese children. The condition is relatively frequent in epidemic form in China and India, but well-developed cases are exceedingly rare in the United States and have not occurred in epidemics. It occurred among infants in Denmark during the First World War when nearly all dairy products were being exported. It is commonest between the sixth and twelfth month and in early adult life. It occurs most frequently in the late winter months.

Xerophthalmia is a consequence of metaplasia of the conjunctiva, causing roughness, and metaplasia of the para-ocular glands, which leads to loss of their secretions and consequent dryness. Infection is secondary.

The earliest sign is drying, roughness, and wrinkling of the conjunctiva and is followed by swelling and redness of the lids, pain, and photophobia. If the lids are held open for a few minutes dry lusterless patches may be observed on the conjunctiva. At the canthi may be seen triangular whitish foamy patches—Bitôt's spots. A light brown pigmentation may develop throughout the conjunctiva. The cornea looses its sensitivity and becomes clouded (see XV*d*, p. 113). Ulcers are liable to form if the condition remains untreated, and softening of the cornea (keratomalacia) may occur with perforation. Panophthalmia then destroys the eye. Hemeralopia is observed in most adults with xerophthalmia and is probably present but overlooked in infants. Characteristic changes in the skin are often present in the older patients. Infants affected by xerophthalmia are usually weak and wasted.

The prognosis in uncomplicated xerophthalmia is good if treatment is prompt and adequate. Otherwise, partial or complete blindness may result. Many of the younger patients die of intercurrent infections. Bloch[8] reported that infants who had had xerophthalmia were particularly liab to infections of the respiratory system, kidney, and skin, and that th mortality was unusually high for as long as eight years.

Prompt diagnosis is obviously essential. It depends upon correct evaluation of the dietary history and of the local signs. Although examination of scrapings from the conjunctiva has been recommended, its value is questioned. Kruse[32] has used the biomicroscope for the detection of early signs. No response or very slow response to treatment with vitamin A is evidence against the diagnosis of nutritional xerophthalmia.

Local treatment with antibacterial substance is indicated if infection is present, but treatment with vitamin A is indispensable. In conditioned deficiency, the intramuscular injection of suitable vitamin A preparations, if available, may be more effective than the use of the newer preparations by mouth. As a result of treatment with vitamin A, luster may return to the cornea in five days and Bitôt's spots may become fragmented and disappear in five or six weeks. All signs of vitamin A deficiency in the eye may disappear in two months.

LESIONS OF THE SKIN

The first complete descriptions of the characteristic dermatosis of vitamin A deficiency were published independently by Frazier & Hu[17] in China, by Loewenthal[35] in Africa, and by Nicholls in India.[41] Lehman and Rapaport[33] described the lesion in American children. The term "phrynodermia" (toad-skin) has been suggested for the dermatosis.[41]

In the cases described by Frazier & Hu, the diet had been deficient for six months to over one year before symptoms began: rice, maize, millet, a little poor-grade wheat flour, white cabbage, and salted vegetables—no meat or eggs, rarely green vegetables. The two youngest patients were 4 and 5 years of age; most of the patients older than 16 years were males. Skin lesions preceded ocular lesions when the latter occurred.

The dermatosis begins with dryness, roughening, and itching of the skin of the whole body (see Figs. I*a*, I*b*, and I*f*, p. 57). Eruptive lesions appear suddenly at the site of the hair-follicles as dry, firm, pigmented papules about 5 mm. in diameter with a central protruding keratotic plug or spine situated below the follicle. The lesions begin on the anterolateral surface of the thighs and the posterolateral surface of the upper forearms and spread. Pustulation occurs in one-third of the cases. The skin assumes a slatey grey color. Comedones are frequent on the face and chest. Histologic studies reveal atrophy of the glandular tissue and hyperkeratosis. The other two manifestations of vitamin A deficiency may be present. The absence of xerophthalmia may indicate a particular predisposition of the skin. All of Loewenthal's cases had hemeralopia.

The dermatosis responds to moderate amounts of vitamin A, slowly to quate diet alone. When the patient receives daily doses of 30 cc. cod er oil, the skin becomes soft and moist in two weeks; xerophthalmia if present disappears in a month; exfoliation of the papules and extrusion of the hyperkeratotic plugs occurs occasionally in a month, and a cure is complete in two or three months. Slight scarring may persist. One patient was cured in fifty-one days when 1 or 2 mg. of carotene was added to his usual diet,[19] indicating that the dermatosis was due to vitamin A deficiency alone. Lehman and Rapaport[31] used a daily dose of 100,000 to 200,000 I.U. of vitamin A. Large doses of vitamin A in alcohol or water-miscible emulsions may be indicated when the deficiency is conditioned.

SPECIAL TESTS FOR VITAMIN A DEFICIENCY

The quantitative measurement of dark adaptation and tests for absorption of vitamin A have recently received considerable study. The direct observation of the conjunctiva with the biomicroscope of Kruse deserves further study.

MEASUREMENT OF DARK ADAPTATION AS A TEST FOR VITAMIN A DEFICIENCY

Night blindness is a frequent early symptom of vitamin A deficiency. Therefore quantitative measurement of dark adaptation under controlled conditions may be of use in the diagnosis of vitamin A deficiency. Two methods have been used: First, *tests* of *distinction:* the measurement of the intensity of the light which the fully dark-adapted eye can just perceive; more particularly, the slight differences in luminosity of objects such as letters or other patterns printed in shades of grey upon a white background, all illuminated by a standard source of light. This method was introduced by Frandsen[16] and by Friderichsen and Edmunds[20-21] in Denmark. In the second method, the eyes of the subject are first exposed to brilliant illumination. During the recovery period in darkness, measurements are made of the intensity of the light which is just perceived. The *time* when the final threshold is reached is obviously important. The final threshold, however, has received more consideration, and it probably has the same significance as the power of distinction. Hecht[25-26] believes that the shape of the recovery-curve, with its two phases, indicates that both the rods and the cones of the retina need vitamin A. For measurements by the second method, the photometer of Birch-Hirschfeld was first used; later, the biophotometer was employed. Hecht used an instrument of special design.

It is obvious, from the study of published reports, that the measurement of dark adaptation requires skill and that the interpretation of the results requires critical judgment. The stimulus must be measurable. The response involves subjective elements; verbal response may not be trustworthy in children aged less than 5 or 6 years. In infants, reliance must be placed on some motor response. There is likely to be variation in response by the same subject and among different normal or presumably normal subjects. A number of consistent results must be obtained before any therapeutic experiment is started. The "learning factor," more or less steady improvement on repetition of the test regardless of treatment, has been clearly demonstrated by Palmer and Blumberg.[42] Experiments should be planned to include adequate controls. If, for example, random variability exists in a group of subjects, and if only the "deficient" subjects receive "treatment," then subsequent tests will certainly show "improvement on the average," whatever the treatment is. If the "nondeficient" subjects also receive the same treatment, it might happen that they actually appeared to become "deficient." Both groups must be treated in order to eliminate the effect of random variability.[27]

Jeans and his colleagues, using the Birch-Hirschfeld photometer and later the biophotometer, reported at first (1933) that 26 per cent of rural children and 53 per cent of town children had deficient dark-adaptation. In 1937,[29] with improved methods, 16 per cent of children were regarded as being deficient. Maitra and Harris,[38] using Jeans' method, stated that no boys in English Public Schools were found to have deficient adaptation, that 22 to 36 per cent of boys in Elementary Schools did have, and that the *treated* boys improved, whereas the untreated did not. Abbasy and Harris[1] took precautions to secure consistent readings and studied both the experimental and control groups, with similar results. Palmer[43] administered 18,000 I.U. of vitamin A per day to one group of children with poor adaptation and 0.05 I.U. of vitamin A to another group with poor adaptation. Improved adaptation occurred to the same extent in each group. These conflicting conclusions indicate the need of caution in the planning and interpretation of the experiments. As a rule, those persons with normal adaptation were not tested again.

Hecht and Mandelbaum[25-26] discuss the significance of the recovery-curve of dark adaptation: the final cone threshold, the final rod threshold, and the time for transition from cone function to rod function. The distribution of these properties in a university population of 110 persons was not affected by sex. Age definitely increases the cone threshold but affects the rod threshold only slightly and the cone-rod transition time not at all. The range over which these properties vary in the population is composed partly of day-to-day variation and partly of individual differences, the latter causing much wider spread. Individual differences are not the result of differences in the vitamin A content of the diet, and with a solitary exception no significant changes were produced by supplementary vitamin A feeding of persons with the highest thresholds. Four young men when deprived of dietary vitamin A responded by a steady rise of both cone and rod thresholds, which were apparent almost from the first day after removal of vitamin A from the diet. After about two weeks of deprivation they showed thresholds above any value normally found in the population; their thresholds continued to rise so long as the deprivation was maintained. The return to a normal diet with or without supplementary vitamin A resulted in an initial small, rapid drop in threshold, followed by a gradual decrease; nearly two months were required for the subjects to return to normal.

Tests for Absorption of Vitamin A

Significant information has been obtained by measuring the quantity of vitamin A, or of carotene, eliminated in the feces after the ingestion of known amounts of these substances. It is assumed that the difference represents the amount of vitamin A or of carotene absorbed. No carotene is ever lost in the urine; no vitamin A is lost in the urine excepting in pregnancy, in fevers, and in some cases of chronic nephritis, and then only in traces. Loss through the skin has not been measured, although it does occur in seborrheic dermatitis and in hypervitaminosis A. Destruction of vitamin A or of carotene may occur in the intestine if unsaturated fatty acids are undergoing oxidation there. The results of this method must therefore be interpreted with caution. The method has demonstrated that mineral oil present with carotene considerably decreases the absorption of the latter; that the cooking of vegetables increases the absorption of their carotene; that small quantities of vitamin A and of carotene are more completely absorbed than large quantities; and that the presence of fat improves their absorption.

In animal experiments, the increase of vitamin A in the liver after the administration by mouth of varying amounts of carotene or of vitamin A is taken as a measure of absorption.

Information regarding absorption of vitamin A can also be obtained by blood analysis after the ingestion of standard doses of vitamin A. The test as originally described by Chesney and McCoord[14] has been widely used. The subject under examination receives such an amount of a concentrated preparation of vitamin A as will provide 7,000 I.U. per kilogram of his body weight. The concentration of vitamin A is estimated in samples of the plasma or serum taken before the dose has been administered and at four, seven, and twenty-four hours thereafter. It has been observed that the maximum rise occurs in normal persons at four hours and that it may be delayed in abnormal persons as much as seven hours. The level at twenty-four hours is usually about twice the normal. The maximum concentration lies between 400 and 800 I.U. per 100 cc. During the test, it is not necessary to discontinue meals, but obviously no vitamin A should be given. Originally, vitamin A ester was used for the test; recently, vitamin A alcohol also has been used. If aqueous dispersions of either form of vitamin A are used, samples of blood should be obtained two and six hours after the dose is given, because absorption takes place more rapidly. Some of the results of application of the test have been mentioned already (see "Absorption of Vitamin A," p. 430). Persons with infectious hepatitis do not absorb vitamin A while the stools are alcoholic unless bile salts are administered. If bile salts are administered together with vitamin A, extraordinarily high levels are observed in the plasma. This phenomenon is probably due to a slower than normal rate of deposition of vitamin A in the liver; it may therefore indicate impairment of one of the functions of the liver.

Absorption tests are of importance in the study of persons who are suspected of having conditioned vitamin A deficiency. Persons suffering from cystic fibrosis of the pancreas, or from lesions interfering with the passage of pancreatic juice into the duodenum, are unable to absorb vitamin A from preparations of the vitamin ester in oils, whereas they can absorb vitamin A from preparations of the alcohol form in oils, or from oily solutions of the ester in the presence of active preparations of pancreatic enzymes; they may absorb vitamin A from very finely emulsified suspensions of the ester in water. Persons with celiac disease or with sprue cannot absorb vitamin A ester or alcohol from preparations in oil. The test therefore has diagnostic value, and may be of aid in selecting the suitable dosage form in treatment. Other conditions have been discovered in which the absorption of vitamin A is decreased: malnutrition following prolonged infections or following diets deficient in vitamin B complex, and ulcerative colitis. In these conditions disorders of motility of the upper small intestine are present and may afford the explanation. Giardiasis[31] may interfere with absorption of vitamin A; it occasionally causes the symptoms of the celiac syndrome. After adequate treatment with atabrin the giardia and the symptoms disappear, and the vitamin A absorption curves become normal.

TREATMENT OF VITAMIN A DEFICIENCY

The materials available for the prevention and cure of vitamin A deficiency include foods, fish liver oils and concentrates derived from them, and preparations of carotene in oil.

As already mentioned, the foods which provide vitamin A activity are: green and yellow vegetables, which contain carotene but no vitamin A as such; dairy products including milk, butter, and cheese, all of which contain both carotene and vitamin A; and eggs, which contain vitamin A. Ordinary mixed diets which include the usual amounts of these foods amply meet the daily requirements of vitamin A. Healthy persons do not need any other sources of vitamin A.

Fish liver oils and concentrates derived from them are so standardized that the dosage-forms provide not over 10,000 I.U. of vitamin A per day. All of these preparations contain vitamin D also. Those mentioned in *New and Nonofficial Remedies* are shown in Table 26.

Viosterol in oil and water-miscible preparations of crystalline vitamin D contain no vitamin A. Polyvitamin mixtures often contain adequate amounts of vitamins A and D. So-called "water-soluble" forms of vitamin A contain solutions of vitamin A in a solvent such as propylene glycol containing a stabilizer; when mixed with water or milk, a very fine emulsion of vitamin A is formed. Carotene in oil furnishes 7500 I.U. of vitamin A per Gm.

When dietary deficiency cannot be discovered in a person with signs of vitamin A deficiency, conditioning factors must be present. They should be treated as already described. If the diet has been deficient, it is necessary not only to prescribe an adequate diet, but also to get the patient to eat it and to continue to eat it after recovery. This may require economic and psychologic measures.

Diet alone will of course cure dietary vitamin A deficiency. In severe deficiency, the more rapid cure by large doses of vitamin A is obviously desirable. In those individuals who are more likely to take prescribed medications than to follow dietary directions, and under circumstances where adequate diet is unobtainable, preparations of vitamin A must be used.

TABLE 26. VITAMIN A AND D CONTENT OF OFFICIAL PREPARATIONS

	I. U.	
1 Gm.	Vitamin A	Vitamin D
Cod liver oil	850	85
Cod liver oil with viosterol	850	360
Blended oils	1800	175
Cod liver oil concentrates	50,000–60,000	5000–6000
Halibut liver oil	60,000	600
Halibut liver oil with viosterol	60,000	10,000
Concentrated oleovitamin A and D	50,000–60,000	10,000–13,000
Percomorph liver oil	60,000	10,000

A review of published experience in the treatment of all forms of vitamin A deficiency shows that the response to a daily dose of 30 cc. of cod liver oil (25,000 I.U. of vitamin A) is usually as rapid as the response to larger doses. It must be pointed out that 30 cc. of cod liver oil contains 2500 units of vitamin D, an amount which is usually harmless. If, however, 100,000 units of vitamin A per day are prescribed in the form of haliver oil with viosterol, oleovitamins A and D, or percomorph liver oil, then 15,000 to 26,000 units of vitamin D are also being prescribed. This amount of vitamin D is possibly dangerous for some children. It would be wiser to use haliver oil or, when available, some other preparation rich in vitamin A and poor in vitamin D.

Reports of the use of carotene in oil in the treatment of vitamin A deficiency are few in number. It is stated that 2 mg. (3300 I.U.) per day are effective. No reports on the use of larger amounts are available.

The purposes of treatment are two: (1) To restore the integrity and function of the affected tissues, and (2) to provide adequate stores of vitamin A. Experience shows that many of the obvious anatomic changes are restored within a period of two months of active treatment with preparations of vitamin A, and all the reversible ones are restored within four months. Calculation indicates that abundant storage should have taken place by two months and certainly by four months. Obviously, blindness from keratomalacia cannot be cured by any measure.

If pathologic changes fail to respond at all after two months of treatment with vitamin A, the failure is due to one of two things: (1) The changes are due to vitamin A deficiency and unrecognized conditioning factors are present, or (2) the changes are not due to vitamin A deficiency. This applies, for example, to such conditions as renal lithiasis and hyperkeratosis pillaris.

Prophylaxis of Vitamin A Deficiency

Normal persons need no supplements of vitamin A, provided they receive an adequate diet. Infants, particularly those of low birth-weight such as premature infants, need supplements of vitamin A from the age of 2 weeks until they begin to get vegetables. Those fish liver oils and concentrates which provide adequate amounts of vitamin D will provide enough vitamin A. After vegetables enter the diet, additional sources of vitamin A are not always necessary; but they are desirable if it is thought that the stores have been depleted by disease. Vitamin D also is required during the entire growing period. For the very rare infant found to be sensitive to fish liver oils, carotene in oil and some preparation of crystalline vitamin D is desirable. The vitamins are best given with meals. The vitamin-containing oils should not be mixed with the formula for an infant, because they are liable to cling to the surface of the bottle or the nipple. Carotene in oil should not be given together with mineral oil, which prevents its absorption.

Prophylaxis in Persons Liable to Conditioned Deficiency of Vitamin A

The underlying condition must be treated when possible: This condition may be, for example, long-continued infection, congenital obstruction or absence of the bile-ducts, postoperative or congenital disorders of the intestine, diabetes, giardiasis, or hypothyroidism.

In cystic fibrosis of the pancreas the following measures are available: (1) Very large doses of vitamin A ester. These may cause slight elevation of the vitamin A of the blood, but the effect is uncertain. (2) Preparations of pancreas, given with the meal containing vitamin A ester.

(3) Vitamin A alcohol. It is well absorbed and need be given only in the usual dose. (4) Dispersions of vitamin A ester or alcohol. (5) Injections of vitamin A. This method has been tried experimentally but is unsuitable for long-continued use and is unnecessary in practice.

In celiac syndrome (including vitamin B deficiency), and sprue both endemic and sporadic, probably the most effective preparations of vitamin A are the fine dispersions, but large doses of ordinary concentrates cause demonstrable increase in vitamin A of the blood. The syndrome itself should be treated by the administration of vitamin B complex and liver extract and by diets low in starch and in fat.

BIBLIOGRAPHY

1. Abbasy, M. A., and Harris, L. J. Tests for partial deficiency of vitamins. Reliability of the dark adaptation test for vitamin A. Abstract of paper read at meeting of Biochemical Society, London, January 14, 1938.
2. Aykroyd, W. R. Beriberi and other food-deficiency diseases in Newfoundland and Labrador. *J. Hyg.* 30:357, 1930.
3. Batchelder, E. L., and Ebbs, J. E. Some observations on dark adaptation in man and their bearing on the problem of human requirements for vitamin A. *J. Nutrition* 27:295, 1944.
4. Blackfan, K. D., and Wolbach, S. B. Vitamin A deficiency in infants: A clinical and pathological study. *J. Pediat.* 3:678, 1933.
5. Bloch, C. E. Blindness and other diseases in children arising from deficient nutrition. *Am. J. Dis. Child.* 27:139, 1924.
6. Bloch, C. E. Further clinical investigations into the diseases arising in consequence of a deficiency in the fat-soluble A factor. *Am. J. Dis. Child.* 28:659, 1924.
7. Bloch, C. E. Light and the A-body. *Am. J. Dis. Child.* 31:315, 1926.
8. Bloch, C. E. Effects of deficiency in vitamins in infancy. *Am. J. Dis. Child.* 42:263, 1931.
9. Booher, L. E., Callison, E. C., and Hewston, E. M. An experimental determination of the minimum vitamin A requirement of normal adults. *J. Nutrition* 17:317, 1939.
10. Booher, L. E., and Callison, E. C. Minimum vitamin A requirements of normal adults. *J. Nutrition* 18:459, 1939.
11. Boyle, P. E. Manifestations of vitamin A deficiency in a human tooth germ. *J. Dent. Research* 13:39, 1933.
12. Breese, B. B., and McCoord, A. B. Vitamin A absorption in celiac disease. *J. Pediat.* 15:183, 1939.
13. Carr, F., and Price, E. A. Color reactions attributed to vitamin A. *Biochem. J.* 20:497, 1926.

14. Chesney, J., and McCoord, A. B. Vitamin A of the serum following administration of haliver oil in normal children and in steatorrhea. *Proc. Soc. Exper. Biol. & Med.* 31:887, 1934.
15. Clausen, S. W. The absorption of vitamin A and its storage in the tissues. *Harvey Lect.* 199, 1942-43.
16. Frandsen, H. Hemeralopia as an early criterion of A-avitaminosis and clinical symptoms and treatment of this disease. *Acta ophth.* 13, supp. 4, 1935.
17. Frazier, C. N., and Ch'uan-K'uei Hu Cutaneous lesions associated with a deficiency of vitamin A in man. *Arch. Int. Med.* 48:507, 1931.
18. Frazier, C. N. and Ch'uan-K'uei Hu Nature and distribution according to age of cutaneous manifestations of vitamin A deficiency. *Arch. Dermat. & Syph.* 33:825, 1936.
19. Frazier, C. N., and Li, H. C. Vitamin A deficiency in man: Resolution of cutaneous lesions following parenteral administration of carotene. *Chinese M. J.* 54:30, 1938.
20. Friderichsen, C., and Edmund, C. A new method for testing the resorption of vitamin A from medicaments. *Am. J. Dis. Child.* 53:89, 1937.
21. Friderichsen, C., and Edmund, C. Clinical experience in the vitamin A balance of children after various diets. *Am. J. Dis. Child.* 53:1179, 1937.
22. Funk, C. The etiology of the deficiency diseases: beri-beri, polyneuritis in birds, epidemic dropsy, scurvy, experimental scurvy in animals, infantile scurvy, ship beri-beri, pellagra. *J. State Med.* 20:341, 1912.
23. Guilbert, H. R., Miller, R. F., and Hughes, E. H. The minimum vitamin A and carotene requirements of cattle, sheep and swine. *J. Nutrition* 13:543, 1937.
24. Hale, F. The relation of vitamin A to anophthalmos in pigs. *Am. J. Ophth.* 18:1087, 1935.
25. Hecht, S., and Mandelbaum, J., Vitamin A and dark adaptation. *J.A.M.A.* 112:1910, 1939.
26. Hecht, S., and Mandelbaum, J. Dark adaptation and experimental human vitamin A deficiency. *Am. J. Physiol.* 130:651, 1940.
27. Isaacs, B. L., Jung, F. T., and Ivy, A. C. Vitamin A deficiency and dark adaptation. *J.A.M.A.* 111:777, 1938.
28. Jeans, P. C., Blanchard, E. L., and Satterthwaite, F. E. Dark adaptation and vitamin A. *J. Pediat.* 18:170, 1941.
29. Jeans, P. C., Blanchard, E. L., and Zentmire, Z., Dark adaptation and vitamin A. *J.A.M.A.* 108:451, 1937.
30. Karrer, P., Morf, R., and Schopp, K. Zur Kenntnis des Vitamins-A aus Fischtranem II. *Helvet. Chim. Acta* 14:1431, 1931.
31. Katsampes, C. P., McCoord, A. B., and Phillips, W. A. Vitamin A absorption tests in cases of giardiasis. *Am. J. Dis. Child.* 67:189, 1944.

32. Kruse, H. D. Medical evaluation of nutritional status: IV., The ocular manifestations of avitaminosis A, with special consideration of the detection of early changes by biomicroscopy. *Pub. Health Rep.* 56:1301, 1941.
33. Lehman, E., and Rapaport, H. G. Cutaneous manifestations of vitamin A deficiency in children. *J.A.M.A.* 114:386, 1940.
34. Lewis, J. M., and Haig, C. Vitamin A requirements in infancy as determined by dark adaptation. *J. Pediat.* 15:812, 1939.
35. Loewenthal, L. J. A. A new cutaneous manifestation in the syndrome of vitamin A deficiency. *Arch. Dermat. & Syph.* 28:700, 1933.
36. McCollum, E. V., and Davis, M. The nature of the dietary deficiencies of rice. *J. Biol. Chem.* 23:181, 1915.
37. McCollum, E. V., Simmonds, N., and Becker, J. F. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. *Bull. Johns Hopkins Hosp.* 33:229, 1922.
38. Maitra, M. K., and Harris, L. J. Nutrition Surveys: Prevalence of vitamin A deficiency among school children at London and Cambridge. *Lancet* 2:1009, 1937.
39. May, C. D., and McCreary, J. F. The absorption of vitamin A in celiac disease. *J. Pediat.* 18:200, 1941.
40. Mori, M. Über den sogenannten Hikan (Xerosis conjunctivae infantum ev. Keratomalacie) *Jahrb. f. Kinderheilk.* 59:175, 1904.
41. Nicholls, L. Phrynodermia: Condition due to vitamin deficiency. *Indian M. Gaz.* 68:681, 1938; 69:241, 1934.
42. Osborne, T. B., and Mendel, L. B. Further observations on the influence of natural fats upon growth. *J. Biol. Chem.* 20:379, 1915.
43. Palmer, C. E. The dark adaptation test for vitamin A deficiency. *Am. J. Pub. Health* 28:309, 1938.
44. Palmer, C. E., and Blumberg, H. The use of a dark adaptation technique (biophotometer) in the measurement of vitamin A deficiency in children. *Pub. Health Rep.* 52:1403, 1937.
45. Sweet, L. K., and K'Ang, H. J. Clinical and anatomic study of avitaminosis A among the Chinese. *Am. J. Dis. Child.* 50:699, 1935.
46. Toomey, J., and Morissette, R. A. Hypervitaminosis A. *Am. J. Dis. Child.* 73:472, 1947.
47. Vitamins. A survey of present knowledge. Medical Research Council Report. London, Stationery office, 1932, p. 234.
48. Wald, G. Series of papers on pigments of the retina. *J. Gen. Physiol.* 18:905, 1934-35; 19:351, 1935; 19:781, 1936; 20:45, 1936; *Nature* 136:913, 1935; 139:1017, 1937.
49. Wald, G., Jeghers, H., and Aramino, J. An experiment in human dietary night blindness. *Am. J. Physiol.* 123:732, 1938.
50. Wolbach, S. B., and Bessey, O. A. Tissue changes in vitamin deficiencies. *Physiol. Rev.* 22:233, 1942.

Chapter 16

VITAMIN D MALNUTRITION AND RICKETS

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RICKETS is a disease of infancy and childhood, but it occurs also, under the name osteomalacia,* in adult life. The features which differentiate rickets from osteomalacia are due merely to the fact that the ends of the bones of children are in a state of active growth. This growth is modified by rickets in such a way as to give rise to swellings, enlargements, and deformities which are never seen in osteomalacia because in the adult person the epiphyseal cartilage does not exist. The fundamental disturbance in both rickets and osteomalacia lies in the calcium-phosphorus metabolism and is of such a nature that calcium salts cannot deposit in anything like the required amount in the growing cartilage or in the new bone which is being formed in the skeleton. The result is that the skeleton becomes weak and unable to withstand the stresses to which it is ordinarily subjected and, in consequence, bends and deforms.

Rickets is a deficiency disease. The deficiency is vitamin D which is essential in the growing child for the normal maintenance of the calcium and phosphorus metabolism. It has, therefore, an exogenous origin. But recent studies have revealed that there are certain forms of rickets which have an endogenous origin, depending on defects in the metabolism and entirely independent of vitamin D supply. These metabolic disorders lower the calcium or the phosphorus concentrations in the body fluids and produce conditions in the skeleton which do not differ in their gross deformities or the pathology from those of D-deficiency rickets. All of these endogenous forms of rickets depend probably on defects in the renal function which directly or indirectly allow calcium or phosphorus to leak out from the body. They all ought to be classified as forms of renal rickets. The disease known as "renal rickets," however, does not, strictly speaking, belong in this category since the changes in the skeleton differ materially from those seen in the deficiency disease. In all cases of renal rickets the lesion in the skeleton is that of osteitis fibrosa, but in many cases, in particular those occurring in young children, cartilaginous changes such as are seen in the true deficiency form of the disease and osteoid production in the shafts are also present. It is difficult to know how to classify renal rickets, which sometimes corresponds completely to osteitis fibrosa but in other cases has in addition the changes characteristic of rickets. "Renal rickets" will not be discussed in this chapter, and the metabolic forms of the disease will be merely mentioned at the end. (See Chapter 10.)

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* For discussion of osteomalacia see Chapter 10, pp. 251-254.

ORDINARY OR DEFICIENCY RICKETS

Vitamin D differs from all other vitamins, so far as known, in that it exists outside the body in certain food substances and can be formed in the body through the action of short ultraviolet radiations. A child can, therefore, receive vitamin D either by eating foods (or substances containing it) or by allowing the ultraviolet light to shine on the body surface.

DIETARY SOURCES OF VITAMIN D

The foods which contain vitamin D are few in number in contrast to the foods supplying the other vitamins. They are, in brief, the fish oils and eggs of all kinds, including of course fish roe. It is important to remember that the muscle meats of mammals—with the exception of the fish-eating mammals like the seal—the cereal grains, tubers, and green leaves do not contain any vitamin D at all. Mammalian liver may contain minute traces. Milk contains very small quantities but not enough to have any protective value against rickets unless vitamin D has been added to it or has been developed in it by means of radiation with ultraviolet light, or unless vitamin D has been fed in large quantities to the cow. Butter does not contain enough vitamin D to make it of any practical value as a source of this vitamin. Hens' eggs (also ducks') do contain vitamin D, but the amount is small, and it is subject to very great variation.

All the fish oils contain vitamin D. In most instances the fish livers are the important sources, as, for example, cod liver oil. But the flesh of such oily fish as the salmon and sardine can be rich in the vitamin. The concentration of vitamin D in the liver varies considerably in the different species of fish. For example, the liver oils of twenty-two different species of fish are richer in vitamin D than cod liver oil. The liver of the blue fin tuna ranked the highest, being 600 times more potent in vitamin D than standard cod liver oil.

Since the fish oils are not natural ingredients of our diets, it is necessary to rely on special preparations in order to obtain protection against rickets. Examples are cod liver oil and the oils from the percomorph fishes. But vitamin D can be produced in oils artificially through radiation with ultraviolet light or bombardment with electrons. Examples are viosterol and irradiated cholesterol. Moreover, vitamin D has been introduced into non-oily vehicles so that it is obtainable in a non-oily form, an example of which is Drisdol. The uses of these various naturally occurring sources of vitamin D and those in which vitamin D has been created artificially will be discussed under "treatment."

The Action of Ultraviolet Rays

There are a number of vitamin D substances produced by irradiation or chemical means which have varying degrees of activity in the prevention of rickets, but only two are of great importance: one of these is viosterol (also known as ergosterol), the other is irradiated cholesterol, known as 7-dehydrocholesterol. The first is the vitamin D of plant origin; the other the vitamin D of animal origin. Viosterol is of great importance therapeutically, but 7-dehydrocholesterol, which is formed by ultraviolet rays in the bodies of human beings and animals, is physiologically more important. Ergosterol has been studied much more than 7-dehydrocholesterol, and its absorption spectrum has been determined. Roughly, it absorbs ultraviolet rays between 315 $m\mu$ and 235 $m\mu$. It is assumed, probably correctly, that the absorption spectrum of 7-dehydrocholesterol corresponds. The provitamin of 7-dehydrocholesterol is omnipresent in our skins and, when ultraviolet rays of the special length mentioned radiate against the skin, they convert the provitamin into vitamin D. It is in this way that ultraviolet light acts in the cure of rickets. The quartz mercury vapor and the carbon arc lamps possess spectrums which cover the entire range of the absorption spectra of vitamin D and extend far beyond. Consequently, when the body is subjected to the emanations of these artificial sources of ultraviolet light the provitamin of the skin is converted into the vitamin in the most efficient manner. Sunlight is also able to convert the provitamin into the vitamin but is far less efficient than the artificial sources of ultraviolet radiations mentioned. The solar spectrum extends on the ultraviolet side only to 290 mμ, and it extends as far as this only under the most favorable conditions of summer. In the winter the shortest solar rays to penetrate to the earth's surface end at 308 mμ. The difference in the amount of ultraviolet light reaching the earth's surface in the summer as compared to the winter is the result of the rotation of the earth around the sun on an oblique axis. In the summer the sun's rays strike the atmosphere surrounding the earth more nearly perpendicularly, whereas in the winter they strike it obliquely even at noon. Thus in the winter time the atmosphere filters out a large proportion of the anti-rachitic ultraviolet rays because they must pass through a greater depth in order to reach the earth's surface. The result is that in the winter sunlight is so enfeebled in the temperate zone as to fail to prevent the development of rickets.

An appreciation of the above facts is important because they explain the seasonal variation of rickets. Years ago Kassowitz[15] and others noted that rickets and infantile tetany were far commoner in the winter and spring than in the summer and fall. This seasonal variation became fully understood when the function of sunlight in protection was realized. A knowledge of the antirachitic role of sunlight makes clear also the geographical variation in the incidence of the disease. For a long time it was realized that rickets was essentially a disease of the temperate zone. It is almost unknown in the tropics, where as the result of the high altitude of the sun all the year round there is a plethora of ultraviolet rays at all times and seasons. Rickets would be a scourge in the Arctic, where the altitude of the sun is so low the year round that few, if any, antirachitic rays reach the surface of the earth even under the most favorable conditions of the Arctic summer, were it not for the fact that the food of the Eskimos, consisting chiefly of fish, seal, and walrus meat, contains amounts of vitamin D adequate for protection. In the Eskimo communities in which our foods have replaced the natural diet rickets has become prevalent.

Before leaving the subject of the relationship of light to rickets, it is necessary to make clear that reflected light from the sun retains the antirachitic properties of the direct sunshine. The sun's reflected rays are known as skyshine while the direct rays of the sun are known as direct shine. Tisdall and Brown[19] have used the following illustration of these two types of "sunshine": If a cylinder were placed over a person and pointed at the sun, the rays reaching the person would be the direct rays or "direct shine." If, on the other hand, the person sat in a window on the northern side of a large building, the only rays which would reach him would be the indirect rays or "skyshine."

It is very important for our health that the skyshine contains antirachitic radiations, for we are dependent on them when the sun is obscured by clouds. In a cloudy country like England the skyshine must be the chief source of antirachitic solar radiation. But though a single shaft of sunlight shining directly on a person, in the back of a room, for example, through an open window would exert a protective power against rickets, skyshine requires a wide expanse of sky so that its radiation can reach the person from many directions. A child placed on a fire escape facing north would receive half the total available skyshine. If he were on top of a mountain he would receive all the skyshine. If he sat in a room indoors lighted by a single open window, he would receive practically nothing in the way of antirachitic rays unless the sun shone directly on him. Rickets is a disease which is particularly prevalent in cities. One reason for this is that a great part of the skyshine is cut off by buildings and also that direct shine fails to reach the bottom of the street. Another reason is that smoke and dust in the atmosphere absorb the ultraviolet light. It is most important to realize that window glass filters out all the effective ultraviolet rays. It is useless to place a child by a closed window, even in the direct sunlight, as a protective measure against rickets because the window glass will insulate him completely. Another reason then why rickets is so prevalent in cities is that more time is spent indoors.

Whether vitamin D is taken by mouth or formed in the skin under the action of ultraviolet light, it is absorbed by the alimentary tract into the blood stream and is distributed to all parts of the body, and the physiologic effect and subsequent mechanism of its action are the same.

There are some other facts in the etiology of rickets which understanding of the action of light makes clear. The Negro child and the dark-skinned southern Italian are far more susceptible to rickets than the white child. The reason for this is that the pigment of the skin absorbs the ultraviolet rays. The dark-skinned races have less sensitive organs for the reception of ultraviolet light than the less pigmented races.

INCIDENCE

Rickets is probably the most prevalent disease known. In a large series of children ranging from birth to 3 years of age, Follis, Jackson and Park,[6] found rickets in more than 50 per cent. The rickets was severe in about 14 per cent, and the very severe degrees were much more common among Negroes. But rickets is still common after the third year. Follis, Jackson, Eliot, and Park[5] have found evidences of the disease in almost 40 per cent of all children dying up to the fourteenth year, the age limit of their study. In the older children, however, the rickets was, with a small percentage of exceptions, slightly developed.

The premature infant is exceedingly susceptible to rickets. Indeed, he is so susceptible that the prevention of the disease is often difficult. One can say that all premature infants will develop severe rickets if not protected by special treatment with vitamin D. The reason for this is the rapid growth and resulting great requirement for calcium. The diminution of growth in the older child and its cessation in the adult are the reasons for the former's milder incidence of rickets and the rarity of osteomalacia in the latter, except during such times as pregnancy or lactation.

Rickets begins to appear during the first month. During the second month its incidence in Follis, Park, and Jackson's unpublished statistics reaches its full height. Because it does not declare itself clinically or by means of the X-ray until the third or fourth month, it is important to realize that rickets may begin shortly after birth.

PATHOLOGY

The characteristic signs of the disease are to be found in the skeleton and result from the failure of calcium phosphate to deposit in the growing cartilage and in the growing bone. As it is calcium phosphate which makes bones rigid, the result is that the skeleton bends and deforms in a variety of ways. When the cartilage fails to become calcified the junctions of the cartilage with the shaft become very weak and the ends of the bones are the first parts to become deformed, mushrooming so that they form knobs which can be both seen and felt. Naturally, the most rapidly growing bone ends are the most affected. Consequently, the knobbing is most marked at the costochondral junctions of the ribs, the lower end of the femur, both ends of the fibula and tibia, and the upper end of the humerus. Next in degree of involvement come the lower ends of the radius and ulna. The lower end of the humerus, relatively speaking, grows slowly, and the upper ends of the radius and ulna grow even more slowly. A knowledge of these facts explains why the deformities of rickets are seldom very marked about the elbow joint. Though the knobbing may be very marked indeed at the upper end of the humerus, it is often not visible because the deltoid hides it. Similarly the knobbing of the upper end of the femur cannot be seen because it is hidden under a thick covering of muscles. Since the lower ends of the radius and ulna and the lower ends of the tibia and fibula are covered only by tendons and skin, their deformity becomes visible very early in the course of the disease even though actually not so marked as that of some of the other bone ends.

As pointed out, rickets is characterized by the failure of calcium phosphate to deposit in cartilage and newly forming bone. Calcium phosphate is not taken from bone already formed, as would be the case if bone were subjected to an acid in a test tube. But, even in health, old bone—both the organic matrix and its complement of salts—is constantly being disintegrated and new bone is constantly being formed. In rickets the destruction of the old lime salt containing bone goes on constantly and sometimes at an accelerated rate. The failure of calcification in the newly forming bone and the destruction of the old lime salt containing bone together weaken the shafts of the long bones. The result is that the shafts of the long bones bend, with the production of bow legs or knock knees in the lower extremities and curvatures in the upper extremities.

The deformities of the long bones really have three different origins. First, the shafts may bend just as a stick bends. Second, on account of their weakness they very often fracture and may become bent from fracture. The fracture may extend all through the bones, or it may be limited to the cortex on one side (infraction). The latter is exceedingly common. The third, and perhaps the most common way in which bending deformities of the shaft of the long bones takes place, is through dislocation of the epiphysis. The epiphysis, on account of the weakness at the cartilage-shaft junction, becomes pulled round on the shaft so that it no longer faces in line with the shaft. Since the new bone formed by the cartilage takes its direction from the cartilage, the new bone is now produced at an angle with the old. One of the best known deformities in rickets is the so-called saber shin. This originates as the result of the tilting backwards of the lower epiphysis of the tibia from the weight of the foot while lying or sitting. At first the curve (angle) which results is not visible except in the X-ray film. When it does make its appearance, it is situated just above the ankle. As more and more bone is produced from the lower epiphysis, the curve keeps occupying a higher position in the leg. In rachitic Baltimore Negro children, aged 4 or 5, the anterior curve of the saber deformity is above the shoe top, and in the adult it lies at about the junction of the lower with the middle third of the tibia.

The deformities of the extremities in rickets bear a definite relationship to the postural habits of the age of the patient, i.e., there are deformities due to lying, sitting, and walking. As already remarked, the saber-shin deformity often begins in the lying period, though it may not be apparent until later. But the deformity of the skull as the result of lying is one of the first symptoms to develop in rickets. As a result of the continued pressure of the brain upon the back of the skull, the latter becomes very thin, giving rise to the symptoms of craniotabes, to be described later. This is due not only to pressure rarefaction of the old calcium-containing bone already formed but also to the quality of the newly formed bone which is entirely lacking in calcium. Often, if the rickets is very severe, the whole back of the head becomes flattened and the head assumes an asymetrical globular shape. When the child begins to sit, he almost invariably crosses his legs tailor fashion, and one will find that the same leg is almost invariably placed over the other one. The effect of gravity on the legs in the sitting position is to pull the epiphyses out of their normal positions with the result that the new bone generated at the epiphyses is at an angle with the old and the most bizarre deformities develop in several different planes. For example, from the effects of sitting on the softened bones one usually finds the femur bowed anteriorly and externally and the tibia bowed anteriorly and also inwardly in its lower part. The total result is the combination of bowed thighs and knock knees which is so characteristic as to make the examiner know at a glance that the deformities were acquired from sitting. In this type of rickets the arms are affected as characteristically as the legs because the child, on account of his weakness, supports his trunk on his outstretched pronated hands. The lower epiphyses of the radius and ulna are always pushed backwards and a little outwards, causing a very conspicuous knobbing deformity. The shafts of both the radius and ulna become greatly bowed. However, the deformity of the arms is seldom so conspicuous or, indeed, so great as the deformity of the legs. In rickets every part of the skeleton is affected, but the small bones, on account of their slower growth, show evidence of the disease only in the X-ray or under the microscope.

The muscular system is also affected in rickets for it becomes relaxed and weak but not so as to give rise to lesions visible under the microscope.

The parathyroid glands are always slightly enlarged in rickets. No lesion in any of the other organs of internal secretion has ever been described.

CLINICAL SYMPTOMS

The clinical manifestations of rickets are subject to great variation, depending on the degree and activity of the rachitic process and on the age, the rate of growth, and the stage of physical development when the disease is active.

CRANIOTABES

The older students of rickets taught that the first symptoms were gastrointestinal disturbances and head sweating. In reality neither of these symptoms is a part of the disease; the first symptoms are the deformities of the skeleton. The earliest to appear is craniotabes which is seen sometimes as early as the second month, becomes quite common in the third month, and disappears usually by the eighth month even though the rickets continues. We have seen this symptom as late as eighteen months. Craniotabes consists of areas of softening of the skull almost always located in the occipital and parietal bones along the lambdoidal sutures. If the infant habitually lies on his side, the craniotabetic areas may be found along the coronal suture, but this is rare. The size of the craniotabetic areas may vary from a spot no larger than the tip of a finger to large areas involving much of the back of the head. Often they are about the size of a quarter. They are rarely symmetrical. To discover craniotabes, with the infant lying on his back, the sides of the head should be held between the palms of the hands and the back of the head explored with the fingertips. Under the pressure of the fingers the skull indents and, often seems to snap back into place when released, with a sensation like that imparted by parchment or by the crown of a derby hat. Craniotabes is most commonly missed when situated low down behind the top of the ear flap just above the mastoid process. It can easily escape detection unless searched for systematically. Craniotabes is more common in premature infants than in those born at full term and, as might be expected, occurs more frequently in winter or spring than in summer.

The question is often asked if craniotabes is pathognomonic of rickets. The answer is "no" because it occurs in conditions other than rickets. However, it is sometimes so characteristic that it is pathognomonic. Craniotabes of a very extensive nature may be present at birth. When such is the case, it is usually situated near the top of the middle of the skull. It is never rachitic, and it usually disappears by the time that rachitic craniotabes becomes manifest. Frequently the skull of a young infant, particularly that of a premature infant, is so thin that it bends under pressure along the suture lines. Giving along the suture lines, where the skull is thinnest, is not craniotabes, although the rachitic skull often can be pushed inwards easily along the suture lines as the result of the diminished rigidity. Sometimes the skull contains spots of unossified membrane, described by Wieland[22] as "congenital holes in the skull." They are tiny things, most apt to occur along the sagittal suture, and ought never to be confused with rachitic craniotabes. Usually they are pathologic curiosities. We have seen craniotabes of nonrachitic origin develop in a baby with rapidly increasing hydrocephalus, but it was situated along the side and front of the head and was easily differentiated from rickets. One is helped in the recognition of true rachitic craniotabes by the discovery that a softening which was not present previously has developed and that the softening extends into the substance of the parietal and occipital bone away from the suture. One is further helped if, without treatment for the rickets, the softening spreads or if, on the other hand, with treatment, the softness disappears. One is aided even more in recognizing that the softness of the skull is rachitic in nature by measuring the calcium phosphorus, and phosphatase levels in the blood, which may reveal that the rachitic state is present. Often also one can establish the presence of rickets by finding the characteristic shadows in the X-ray film of the long bones of the extremities (see XII*b*, p. 101).

The anterior fontanel does not close at the usual time in rickets and, in some cases, it actually expands. It is frequently found open at 2½ years as a result of rickets but usually becomes closed by the end of the second year, even if the rickets continues. The margins of the rachitic fontanel are soft and can be bent inward. This is a differential point of some importance because when the fontanel remains open in cretinism (as it does sometimes even to the seventh year), or in congenital malformations of the skull, the cranial bones which form the margins of the fontanel remain firm.

If the rickets is severe, the margins of the cranial bones forming the sutures are soft and can be readily pressed inwards with the finger. The margins may seem separated since they are so lacking in calcium phosphate that they cannot be felt and are taken for intersuture material.

Thus far we have dealt with thinning and softening of the calvarium, but the latter can become greatly thickened in rickets. In the skull of a baby with very severe rickets and also severe secondary anemia, the thickness of the skull cap at its thinnest point was 1 cm., and at its thickest the frontal eminences measured 2 cm. Thickening of the cranial vault is usually most marked at the frontal and parietal eminences, constituting the so-called rachitic "bossing of the skull." The thickening is due to new bone formation from the periosteal surface. When the thickening of the frontal and parietal bosses is very marked so as to produce actual deformity, the condition is called caput natiforme or the hot cross bun head. The hot cross bun appearance is due to the fact that the frontal and parietal eminences appear as mounds, separated from each other by the grooves following the coronal and sagittal sutures. If the thickenings of the frontal eminences run into each other, the effect is to make the forehead as a whole very prominent and project unduly beyond the plane of the face. The deformity is then spoken of as the olympic brow. The olympic brow occurs also in congenital syphilis even to a more marked degree than in rickets.

It is very common to find thickening and thinning of the skull occurring together in rickets. The parietal and frontal eminences may be greatly thickened whereas the back of the skull may be greatly thinned and the seat of extensive craniotabes.

Often in rickets, particularly in prematurely born infants, the anterior fontanel may bulge slightly. But true obstructive hydrocephalus never occurs as a part of rickets.

TEETH

The primary dentition may be delayed by rickets, and the disease often causes the teeth to erupt out of order. It is common for a rachitic child to have only 2 teeth or none at all at the end of a year. Ultimately the deciduous teeth erupt in spite of the rickets. But rickets does not produce defects in the enamel of the deciduous teeth.

Rickets affects severely the permanent teeth which are in process of formation during the rachitic disturbance in calcification (see VIII*d*, p. 85). The injury to the teeth takes the form of deficiencies of enamel, evidenced by thinning, pitting, grooving, or actual absence. The loss of enamel may be so great as to affect the whole surface of the incisor teeth or, more usually, the surface distal to a certain line, the line demarcating the level of growth at which the rickets stopped.

THORAX

Next to craniotabes, the earliest sign to make its appearance in rickets is enlargement of the costochondral junctions. Individually the enlargement is referred to as "beading of the ribs," but since the beads in their entirety extend in chain fashion down both sides of the thorax together, they are called "the rachitic rosary" (see XV*b*, p. 113). The beads vary in size according to the severity of the rickets, from swelling scarcely exceeding the normal enlargement to elevations half a centimeter high and one or more centimeters in length. They are very conspicuous in thin children, mounding up the overlying skin, but in obese children they may not be seen, though they can be felt. When the costochondral junctions sink inwards as is the case when the arch of the rib is so weakened that it yields to atmospheric pressure and becomes permanently inverted, the prominences of the beads disappear and a trough develops marking their site. They can be felt, however, on the floor of the trough. When the sides of the thorax are pushed inwards, the sternum becomes thrust forward, forming a ridge or a promontory which is known as the rachitic pigeon breast. Rickets by itself rarely gives rise to a very great pigeon-chest deformity. The deformity reaches its greatest development as the result of interference with inspiration caused by adenoids, particularly when there is an associated rickets. However, the nasal obstruction from adenoids can produce marked pigeon breast even when no rickets is present.

If the rickets is severe, the bony part of the thoracic cage becomes greatly weakened with the result that it is pulled out of shape by the various muscles attached to it. One of the best examples of deformity due to muscle pull is the so-called Harrison's grooves. These are depressions in the sides of the thorax at the level of the diaphragmatic attachments. With each inspiration the diaphragm draws the lower lateral parts of the thorax inward until ultimately permanent deformities in the form of horizontal grooves make their appearance. The grooves are intensified by the abdominal distention so commonly accompanying rickets, which causes the abdominal aperture of the thorax to flare outward at the side like a corset. The thorax is also pulled out of shape upwards by the accessory respiratory muscles of the neck. In very severe rickets the neck, when viewed from in front or the side, has the appearance of being much shortened because the thorax is drawn close under the chin.

In rare cases the thorax may be so weakened from the effect of the rickets on the ribs that its function as a bellows becomes greatly impaired and its lack of rigidity may actually cause the death of the child. In such cases the inspiratory effort seems to result in a caving in of the thoracic cage to such degree that the circumference of the chest may be diminished. Respiration is made possible only through diaphragmatic action. But the diaphragm expends much of its energy in drawing in its attachments and so operates at a great disadvantage. We have seen a rachitic baby with respirations 150 per minute, though suffering only from bronchitis.

SPINE

The spine becomes deformed in rickets posturally but not in its actual structure. When the child sits, a rounded kyphosis develops in the dorsolumbar region or less commonly in the dorsal region. This kyphosis disappears when the child is held up by the shoulders with the body pendant, in contradistinction to the kyphosis of Potts' disease. When the child with rachitic kyphosis attains the standing period, the kyphosis disappears entirely and a lordosis takes its place. The lordosis on standing, in rickets, is also postural. It is situated low down, just above the buttocks, causing the latter to appear to stick out. The rachitic lordosis occupies a lower position than the relaxation lordosis in hypotonic children and is the obligatory result of the rachitic deformities of the pelvis and legs which cause the trunk to arch sharply backward in order to bring the weight of the trunk over the legs.

Long Bones

Rickets produces enlargement of the ends of the long bones. If the rickets is severe, the enlargements may become so great as to leave no doubt of their rachitic nature. Unfortunately, however, the size and shape of the bone ends of the arms and legs vary considerably in different children. This factor of variation in size and also shape is the cause of many an erroneous diagnosis of rickets. The bone ends, which are the best suited for the recognition of rachitic enlargement and, hence, which are most useful for diagnostic purposes, are those of the ulna and radius at the wrists and the fibula and tibia at the ankle. As already indicated, they are not the bone ends most affected by the disease but owe their clinical importance to their light covering by superficial tissue. The upper end of the humerus and of the femur are too deeply covered by muscles for enlargements to become either visible or palpable unless extremely developed or the soft parts emaciated, and the bone ends forming the knee joint are too large for rachitic increases in size to result in easily recognized contour changes.

Marfan described a change in contour of the external malleolus which he thought diagnostic of rickets in its early stages (Marfan's sign). When the finger strokes the external malleolus of a young healthy child downwards, one can feel the junction of the shaft of the fibula with the cartilage as a single, barely perceptible elevation. When the lower end of the fibula becomes the seat of rickets, the stroking finger has the sensation of feeling two elevations, one corresponding to the cartilage-shaft junction and the other to the epiphyseal cartilage below. In the writer's experience, this sign of rickets is not more trustworthy nor does it make its appearance earlier than enlargements of the costochondral junctions and the lower ends of radius, ulna, tibia, and fibula. When the rickets is very severe, the lower ends of the radius and ulna and of the tibia and fibula may form veritable knobs and, under those circumstances, the enlargements of the lower end of the femur and the upper end of the tibia and of the upper end of the humerus are also visible. In very severe rickets, the knee has a double-jointed appearance due to the fact that the enlargements of the lower end of the femur and upper end of the tibia are so great that the joint looks constricted. In Germany and in Holland in early times rickets was known as the double-jointed disease.

As already pointed out, the shafts of the long bones may be curved in various directions, depending on the age at which the rickets was acquired. If the rickets develops after the second year, i.e., if the bones give way as the result of standing, the curvatures of the legs are apt to develop in the lateral plane. Bow legs are referred to in the German literature as the "O" deformity. When the O deformity is entirely in the lateral plane, one can often be sure that the rickets is, relatively speaking, a late development. The same applies to knock knees or the "X" deformity. One can often be sure that the rickets was already developed in the lying and sitting periods from the presence of the anterior bowing of the lower ends of the tibias, forming the rachitic saber-shin deformity, also carrying with it bowing of the femurs forwards and outwards. As already indicated, the deformities acquired in both the arms and the legs from sitting are very complicated since the bones are bent in different planes and places, yet they almost always follow absolutely characteristic patterns.

When the child with severe rickets begins to walk, the gait has a characteristic waddling appearance. This used to be explained by the effect of rickets on the neck of the femur which causes it to bend downwards so as to form a right angle with the shaft. The symptom is known as the coxa vara deformity of rickets. However, this alteration in the direction of the neck of the femur does not explain the waddling gait, which is caused by a twist in the tibia and femur. In all probability the twists come about as the result of gradual postural rotation of the cartilaginous epiphyses of the shafts, or in other words the bone is twisted during growth rather than deformed after the growth has been completed. As a result of the twists, the posture of the legs is much altered, though this is not readily apparent until the child walks. In order to keep the feet parallel in the anterior-posterior direction, it is necessary that the femora at the hip joint be in a position of external rotation. In this position the hip joint is deprived of the stabilizing pull of the gluteus medius and minimus. With the action of these muscles impaired, the support of the trunk on the femur is weakened. As a result, the child compensates by bringing the weight of the body with a poising movement over each leg in turn as the leg assumes the weight bearing. The waddle is not so extreme as in cases of congenital dislocation of the hip, but its cause is analogous.

The pelvis is also affected in rickets. The thrust of the femur causes the part of the pelvis containing and surrounding the acetabulum to become pushed upwards and inwards with the result that the pelvic outlet becomes narrowed. Moreover, the sacrum becomes much arched and pushed forward, further narrowing the pelvic outlet. If the rickets is of short duration, the pelvis is not permanently injured. The cases in which the pelvis is so deformed as a result of rickets that it furnishes an obstruction to childbirth are those in which the disease has probably persisted for years.

NONSKELETAL CHANGES

Rickets is not a disease of the skeleton only, for it also affects the muscles though it does not produce changes in the latter which are recognizable under the microscope. The relaxation of the muscles is one of the causes of the enlargement of the abdomen known as the rachitic pot belly. A further cause of the pot belly is the constriction of the lower part of the thorax. Other evidences of the muscular relaxation are the dorsal kyphosis and the flat foot. Occasionally the hypotonia is so great as to permit hyperextension as in Mongolian idiocy.

The motor performance in rickets almost always shows a lag due to the effects of the disease on both the muscles and the bones. A rachitic child may not be able to sit unsupported at a year or even 18 months of age and often cannot walk at 2½ years and occasionally not at 3 or 4 years. Trousseau,[20] in his superb description of rickets, describes many children who remained bedridden for years as a result of the disease. Not only is sitting or walking delayed, but the process of learning is strung out over a long period. Muscular activity may not always be affected in any very obvious way. We have seen a 10-year-old child suffering from rickets of long duration who could skip rope like an ordinary child.

It has been already pointed out that the premature infant is extraordinarily susceptible to rickets, that the disease begins very soon after birth, and advances with great rapidity. However it often fails to give rise to physical signs which are at all proportionate. In the premature infant rickets is particularly apt to show itself in the head. Craniotabes is very common and, if the baby lies on its back all the time, the back of the head becomes flattened and the forehead pushed forward. The extremities often seem to be little or not at all affected. This is probably due to the fact that the premature infant moves the body only slightly so that stress and strain have little opportunity to produce deformity.

Severe rickets can occur in the older child and is then known as late rickets (rachitis tarda). Beginning late or early, it may persist even into adult life. When either of these contingencies happens, it is probable that some special inherent susceptibility to the disease exists. When rickets continues for a long period after early childhood, its early incidence can usually be recognized by the presence of deformities characteristic of the sitting period. When, however, rickets develops after the second or third year, the only symptoms may be the development of knock knees or bow legs or the presence of more curvatures in the shafts of the long bones than enlargement at the ends. Of the cartilage-shaft junctions, growth lasts longest in the ribs. Enlargement of the costochondral junctions may occur when the ends of the long bones of the extremities show no alteration. Late and infantile rickets are the same disease, the difference being only symptomatic.

Stunting of growth by rickets may be extreme. Adult rachitic dwarfs, for example, may be as little as four feet in height. In the rachitic dwarf the disease nearly always, if not always, goes back to infancy, and its early origin is declared by the persistence of the pattern of deformities characteristic of the sitting stage. The arms of the rachitic dwarf are usually disproportionately longer than the legs. The cause of the dwarfing is probably twofold. As the result of the rickets the soft bone formed from the cartilage is flattened out and fails to add to the linear growth. Also, the curvatures of the legs result in losses in height. But, in all probability, the actual proliferation of the cartilage becomes diminished in rickets. We know this to be the case in the artificially induced rickets of rats, and it is probable that the same holds for the human being.

X-RAY CHANGES

The X-ray is of the greatest possible use in the diagnosis of rickets, but it does not reveal the disease in its early stages. When rickets is visible and can be recognized in the X-ray film, one can be certain that the disease is in an advanced state of development.

The characteristic X-ray changes produced in the bones by rickets occur both at the cartilage-shaft junctions and in the shafts. The changes at the cartilage-shaft junction are characterized by cupping, spreading, fringing, and stippling (see XII*b*, p. 101). Since the epiphyseal cartilage is virtually transparent in the X-ray film, the calcium-containing end of the shaft is silhouetted. Cupping is present when this is concave. But cupping occurs only at those shaft ends whose normal configuration is favorable to that development. The lower end of the radius, both ends of the tibia, and the lower end of the femur do not show cupping until the rickets is advanced, but both ends of the fibula and the lower end of the ulna which are slightly cupped anyway show the cupping effect of rickets early. Cupping is due to the fact, as already emphasized, that the cartilage-shaft junction in rickets is very weak and gives way under stress and strain with the result that the columns of cartilage cells become fanned out peripherally. Hence the shaft forms along the sides of the proliferative cartilage, seeming in the film to embrace the latter in cup fashion. Cupping may be seen in scurvy and is often very pronounced in chondrodystrophy.

Spreading of the end of the shaft may accompany cupping or it may exist by itself. It is caused, like cupping, by weakening of the cartilage-shaft junction which causes the cartilage columns to be pushed out laterally, with the result that the end of the shaft becomes extended laterally, i.e., becomes pushed out and broadened.

Fringing consists in thread-like shadows extending from the end of the shaft into the transparent cartilage. The threads are caused by extension of calcium-phosphate-containing tissue either from the interior of the shaft itself or from the cortex or from both, into or around the cartilage mass or its adnexa of uncalcified and hence transparent tissue.

Stippling is a very valuable sign. It is present when the outline of the end of the shaft has an irregular, dotted or spotted appearance. Very commonly, particularly when the rickets is only partially developed, calcium-phosphate continues to deposit at certain points only. The result of this development of isolated masses of calcium-phosphate-containing tissue gives rise to the stippled appearance.

The finer changes in the shaft are less definite than those of the cartilage-shaft junction and lead to the diagnosis of rickets only when extremely developed. The characteristic feature is that the trabecular meshwork becomes very coarse and may vary in design in different parts of the bone. In very severe rickets there is a great loss of density in the bone due to two factors; (1) the failure of calcium-phosphate deposition in the newly formed bone, and (2) the destruction of the old, which was completely calcified before the rickets began. In the severest degrees of rickets, the shafts cast only the most feeble shadows and appear ghosts of themselves. In advanced degrees of the disease, the cortex may appear abnormally thin or not show at all so that the edge of the shaft has a ragged appearance or hair-like shadows may stick out from the sides. On the other hand the cortex may appear to be greatly thickened and reduplication of the cortex can be seen, one cortex envelopment lying outside another. When the cortex is hypertrophied, the marrow cavity is often reduced in size or becomes eccentric. It is very common in rickets for several cortices, not suspected as existing, to come to light when the disease is treated. Of course the curvatures of the long bones caused by rickets are very characteristic in the X-ray film.

Often when rickets cannot be definitely recognized under the X-ray, treatment will declare its presence by bringing out an end of the shaft which previously did not cast a shadow and, in consequence, was never suspected of existing. It is very characteristic in severe cases of rickets for lines of calcium-phosphate to make their appearance well in advance of the shaft. It was pointed out years ago that when rickets heals, calcium-phosphate deposits in the stratum of cartilage in which it would have deposited if rickets had never been present at all. The line of calcium-phosphate lying in advance of the end of the shaft in the X-ray film is in reality the provisional zone of cartilage, permeated with lime salts, visualized on edge and marking the level which the shaft would have reached if the rickets had not supervened.

BLOOD CHEMISTRY

A great advance in the knowledge of rickets was made when Iverson and Lenstrup[12] and Howland and Kramer[10] at the same time found that deficiency rickets was in a great majority of instances characterized by a lowered plasma phosphorus. In the healthy infant the plasma phosphorus is 5±0.5 mg. per cent per 100 cc.; in the healthy adult from 2 to 3.7 mg. per cent per 100 cc. In infantile rickets the phosphorus usually lies between 2 and 4 mg. per cent but may be reduced to 1.2 mg. per cent or even less. In the infant 4 mg. per cent represents an intermediate value between the rachitic and the normal state.

The calcium is usually found at the normal level of 9.5 to 11 mg. per cent. The calcium of the plasma may be lowered in rickets together with the plasma phosphorus or, while the phosphorus level remains normal. One may find, for example, an inorganic calcium of 8 mg. per cent with an inorganic phosphorus of 2 to 4 mg. per cent, a condition often encountered in a premature infant. But the calcium may be reduced even to as low a figure as 5 mg. per cent. Part of the calcium is bound to the protein of the blood and, when the plasma protein is reduced, the calcium is correspondingly reduced. The ionized calcium is represented by that part not bound by the protein, so that when the calcium is found to be low in the plasma, it does not follow that the ionized calcium is reduced. When, however, the plasma calcium is reduced below 8 mg. per cent, tetany is frequently found in addition to rickets.

It is important to realize that in the premature infant and perhaps in the extremely young fullterm infant, rickets can develop in the presence of calcium and inorganic phosphorus concentrations which fall within the range regarded as normal. For example, we have seen the development of rickets in a premature infant whose plasma calcium measured 10 mg. and inorganic phosphorus 6.4 mg. per cent. The reason for this is that in the premature infant the new formation of bone goes on at such an accelerated rate that the requirement for calcium is, relatively speaking, enormous, and there is not enough calcium absorbed to meet the requirements of the skeleton even though the concentration of phosphorus is maintained at a higher than normal level.

Howland and Kramer[11] developed an empirical formula for determining the presence or absence of rickets based on the product of the calcium and the phosphorus values. If this was under 30, rickets must be assumed to be present; if over 40, rickets was not present, and if the product lay between, rickets might or might not be present. As already mentioned in the case of the premature infant, this formula has a limited value, particularly when it is considered that the inorganic phosphorus of the adult lies within the range of rickets in the infant, yet the adult does not suffer from the disease.

The healthy breast-fed infant retains from 50 to 60 per cent of the intake of calcium and phosphorus and the healthy artificially-fed infant from 30 to 50 per cent. In the infant with active rickets the retention of calcium and phosphorus is greatly diminished, but only exceptionally does the balance become negative. The phosphorus in the stools is increased, and the phosphorus excreted in the urine usually but not always is diminished. The calcium excretion in the stools is greatly increased and the calcium excretion in the urine is diminished and may disappear altogether, though the amount lost in the urine in health is so small as to make the reduced excretion in rickets of no importance. When vitamin D is administered, the calcium and phosphorus metabolism is rapidly restored to normal and as much as 60 to 80 per cent of the calcium and phosphorus ingested may be retained.

No one knows exactly what the function of alkaline phosphatase is with reference to the calcium and phosphorus metabolism. But it is increased in rickets, and the phosphatase measurement has been used for the detection of this disease. In the child who is healthy, 5 to 15 Bodansky units are regarded as normal. In rickets the phosphatase is increased to from 20 to 60 units or even more. Of course the phosphatase is increased in a whole variety of conditions which have no relation to rickets, among them hyperparathyroidism, osteitis deformans, malignant growths of the skeleton, diseases of the liver, Graves' disease, and in pregnancy. It is decreased in malnutrition, hypothyroidism, and scurvy.

PATHOGENESIS

No one knows what the function of vitamin D is although some of its effects are apparent. It increases the absorption of calcium and phosphorus from the intestine; this is perhaps to be regarded as its most potent action in the prevention and cure of rickets. In the rachitic person the renal threshold for phosphorus excretion is lowered.[9] Vitamin D increases the reabsorption of phosphates by the kidney from the glomerular filtrate so that it reduces the amount of phosphate lost in the urine. When given in large amount it acts upon the osteoblasts, breaking down bone and liberating calcium and phosphorus. In these three ways it regulates the calcium and phosphorus metabolism of the body and causes the body to operate with a greatly increased economy. Relatively speaking, the requirement for calcium-phosphorus of the young child is very great in order to meet the needs imposed by the rapid expansion of the skeleton. If vitamin D is not supplied, the calcium and phosphorus metabolism becomes deranged; the calcium and phosphorus of the food which is absorbed from the gut diminishes, and the phosphorus is excreted at a lower threshold by the kidney and, presumably, the calcium and phosphorus overturn in the skeleton ceases to be regulated with physiologic nicety. As a result the supply of calcium and phosphorus to the skeleton falls short of the requirements while growth of the skeleton continues, the result being the development of rickets.

The reason that the serum phosphorus falls in rickets and the calcium is maintained at a normal level is thought to be due to the activity of the parathyroid glands, i.e., in the absence of adequate absorption of calcium and phosphorus from the intestine, the normal-calcium–low-phosphorus equilibrium maintained in the blood plasma is attributed to the regulatory influence of the parathyroid glands which may lower the threshold of excretion of plasma phosphate via the kidney while maintaining the calcium plasma level at its normal height. When the parathyroid mechanism ceases to be sufficient, the calcium falls and infantile tetany makes its appearance. It should be noted that the explanations offered above take no note of the possibility that there are local factors in the nature of enzyme systems which are determinants in calcification. It is probable that the action of vitamin D is concerned with them also and perhaps plays its most important part in these local processes.

PREPARATIONS OF VITAMIN D

Cod Liver Oil

According to the U.S.P., cod liver oil must contain not less than 85 I.U. per gram, though most cod liver oil marketed in this country contains at least 100 I.U. per gram. One teaspoonful of cod liver oil (4 Gm.) supplies at least 400 I.U. The vitamin in cod liver oil is 7-dehydrocholesterol, the same as the one formed in the skin through radiation. Cod liver oil contains vitamin A (U.S.P. minimum requirement 850 I.U. per gram) as well as vitamin D. The disadvantages of cod liver oil are its fishy taste and the requirement for rather large dosage. It is not practical to give more than 4 teaspoonfuls (1600 I.U.) daily. Therefore, cod liver oil is not serviceable when large intakes of vitamin D are essential. Its fishy taste is not an objection in the case of young infants, who quite generally like it provided the person administering the oil does not prejudice them against it. Objection to the use of cod liver oil is the belief that it causes digestive disturbances in hot weather or that the infant is constitutionally unable to take it. These objections rarely have any basis. However, if aspirated, it will produce lipid pneumonia. Therefore, cod liver oil should never be given to premature infants, to very sick infants, or to infants who for one reason or another might aspirate the oil.

Viosterol in Oil

The U.S.P. requires that 1 Gm. of viosterol in oil shall contain 10,000 I.U. of vitamin D. One drop contains 200 to 222 I.U. Viosterol is tasteless. It can be dropped directly into the mouth of the infant or administered in orange juice on a teaspoon and floated into the mouth. It should never be added to the feeding lest a part adhere to the bottle and be lost. It does not supply vitamin A. Ordinarily viosterol is furnished in an oily solution. However, it is also supplied in the medium of propylene glycol. The advantage of propylene glycol as a vehicle is that the viosterol mixes with the milk and can be introduced with safety via the food.

Enriched Fish Oils

These all are made up to correspond in strength to viosterol in oil, namely 1 Gm. contains 10,000 I.U. and 1 drop 200 to 222 I.U. These preparations all contain vitamin A in addition to vitamin D. In percomorph oil, for example, there are 60,000 I.U. of vitamin A per gram. The possession of vitamin A in these concentrated preparations of vitamin D has the advantage of conferring dual properties. However, it is necessary to realize the danger of the presence of a large quantity of admixture of A when enormous doses of vitamin D are required as is the case in certain forms of refractory rickets. Twice we have encountered vitamin A poisoning when these preparations were used in extremely large doses.

Irradiated Cholesterol

This produces 7-dehydrocholesterol, the vitamin D from animal sources, which is highly effective. The activation is regulated so that each gram contains 10,000 units.

Vitamin D Milk

This is produced through the addition of crystalline vitamin D, vitamin D concentrate, or by the exposure of milk to ultraviolet light from artificial sources. The milk is standardized so that it has a potency of 400 I.U. per quart. Vitamin D milk is marketed fresh and also in evaporated and dried forms. The taste is not impaired by either of these processes. In some states the potency is well controlled.

VITAMIN D REQUIREMENTS

The lowest dosage advocated by Jeans, Stearns, and their associates[13, 14, 17, 18] is 400 to 600 I.U. of vitamin D. This dosage is inadequate to prevent the development of rickets in susceptible young infants. As already pointed out, the premature infant is particularly prone to develop rickets, and the dosage of 400 I.U. is totally insufficient to prevent the disease in his case. It seems wisest to place the dosage of vitamin D for the young infant at 800 I.U. daily. In the case of the premature infant, no one knows what the requirement of vitamin D for protection against rickets actually is. It is probably subject to great variation, but certainly in the early months as much as 2000 I.U. in the form of viosterol or one of the concentrates should be given.

In the case of the infant after the first year, the protective dose may be placed at 400 I.U. daily. Because Follis, Jackson, and Park,[5] have shown that rickets continues to puberty, though usually in a mild undetectable form, it is advisable to continue the administration of vitamin D throughout the period of childhood. The easiest way in which this can be accomplished is through the use of activated milk. Probably a very small amount of vitamin D is adequate to prevent the development of rickets in the older child.

VITAMIN D THERAPY IN RICKETS

Three teaspoonfuls of cod liver oil or 1200 I.U. of vitamin D daily will bring about the cure of rickets in all ordinary cases. The deposition of calcium-phosphate in the bones can be seen quite regularly in the X-ray film on the twenty-first day. Any dose of vitamin D which will prevent the development of rickets will cure the disease if a sufficient amount of time is allowed to elapse, but it is advisable to give larger doses of vitamin D in order to cure rickets promptly. When the rickets is over, the dosage can be reduced to protective levels. In general, as a temporary measure for the cure of rickets, it is advisable to give approximately 5000 I.U. of vitamin D in any accredited form daily. The effect of the treatment can be followed by means of the X-ray and the calcium and phosphorus measurements in the plasma. The shadows at the ends of the bones caused by the deposition of calcium-phosphate make their initial appearance between the fourteenth and twenty-fourth day of treatment, and the ends of the bones in very severe rickets will be found to be rather well filled in by the end of five to six weeks. The calcium and phosphorus levels in the plasma are affected and begin to rise about the beginning or end of the third week of treatment. The depositions in the bones precede this elevation of the calcium and phosphorus in the plasma. When the bone ends have filled in—the normal trabecular pattern will not be restored in severe rickets for six or more months—the treatment should be dropped back to the preventive level of dosage. If X-ray and laboratory facilities are not available, it is entirely safe under ordinary conditions to continue the dosage of approximately 5000 I.U. for five to six weeks. But the susceptibility to the disease is subject to considerable variation, and the dosage of the vitamin required is more in some cases than in others. The dosage needed can be determined by a trial and error policy. In one of our cases it was necessary to use 60,000 I.U. daily in order to produce a therapeutic effect. If the rickets is severe, there is no danger in the use of dosages of 10 or 20,000 I.U. daily until the cure is effected.

Single Massive Doses of Vitamin D

Vollmer[21] was the first to advocate treatment of rickets with the single massive dose of vitamin D. The massive dose may be given orally, but hypodermic injection is to be preferred. For oral administration a single dosage of 300,000 to 600,000 I.U. in specially prepared, highly concentrated form, is usually employed. If oral administration is employed, great care must be exercised that there is no loss of the vitamin from adherence to the receptacle employed. For hypodermic injection, Vollmer advocates 600,000 I.U. of vitamin D. Special preparations of vitamin D must be obtained for hypodermic use. In a recent case of ours in which 600,000 I.U. of vitamin D was given parenterally, calcium-phosphorus deposition could be detected in the skeleton ten days afterwards. The calcium-phosphorus levels in the blood were not altered until four days later and then only slightly. For the prevention of rickets in the premature infant, Freudenberg[7] recommends a single parenteral dose of 300,000 I.U. In a personal communication he informed the writer that he had had the opportunity to examine the tissues of the premature infants treated in quite a large number of autopsies and had failed to find the slightest evidence of any bad effect.

The use of the massive dose treatment of the premature infant has the great advantage of conferring protection by means of a single manipulation for three to four months, and it probably constitutes the best method for the protection of the premature infant from the disease. This form of treatment is useful, also, in all cases in which there is danger that the daily administration of vitamin D will not be carried out as in situations in which the negligence or stupidity of those responsible is too great for them to be trusted or in which daily oral treatment is inadvisable from any cause. But it is certainly wiser from the educational point of view not to deprive those in charge of the child of the responsibility for the complete care of the child, including the prevention of deficiency diseases. If the physician takes away the responsibility for the prevention of rickets from the parent, it becomes his duty to see that the preventive treatment is carried out to the limit of requirement even if the infant is removed. This is a greater responsibility than he has time to undertake except in certain special instances.

THE CITRATE TREATMENT

It was shown by Hamilton[8] and Shohl[16] independently that rickets could be cured through the oral administration of a mixture of sodium citrate and citric acid. They added 30 cc. molar sodium citrate and 20 cc. molar citric acid* to the formula daily.

The cure of the rickets under this treatment will take place at about the same rate as when large dosages of vitamin D are employed. No knowledge exists at the present time in regard to the modus operandi of the citrate treatment. Though this method of treatment can be employed for the cure of rickets, it should not be employed for the prevention of the disease. Rickets can be cured by means of orange juice if sufficient (according to Shohl and Butler 600 to 700 cc. daily) is given.

It is very difficult to determine by physical examination alone that the treatment of rickets is successful. The most satisfactory method generally available is by means of X-ray film in which the shadows produced by the healing process are readily apparent. The earliest that they ever make their appearance is probably eight to ten days after treatment has been begun. But, if the treatment is adequate, they surely ought to be visible at the end of three weeks. In severe rickets the first clearly defined change is the development of a transverse line of shadow, usually broken, making

* $H_2C_6H_5O_7 \cdot \frac{1}{2} H_2O$, 219 Gm. per liter. $Na_3C_6H_5O_7 \cdot 5\frac{1}{2} H_2O$, 357 Gm. per liter; $Na_3C_6H_5O_7 \cdot 2 H_2O$, 294 Gm. per liter.

its appearance just beyond the end of the shaft. As treatment continues this line becomes thicker and more dense and splotches of shadow often longitudinal, occur in the gap between it and the end of the shaft until the gap becomes completely filled with lime salts. The filling in process may take two months, and the rachitic pattern may still be visible for months. At the same time periosteal coverings, the existence of which was never suspected, come into view and the texture of the shaft acquires an increased density.

A sure way to determine the effectiveness of the treatment is through the chemical estimations of the calcium and inorganic phosphorus of the blood. After from ten days to three weeks of treatment the phosphorus rises to the normal or nearly to the normal level. The phosphatase remains elevated after brisk calcium-phosphate deposition has been in progress for some time but gradually sinks over a period of weeks to the normal level. Clinically, after three weeks of treatment, the baby seems more alert and begins to use his body, standing or trying to walk. The nurse may say he is better before the doctor can discover objective signs. Very gradually the enlargements at the ends of the bones diminish.

ULTRAVIOLET RADIATION FROM SUNLIGHT OR ARTIFICIAL SOURCES

Exposure to sunlight in the summertime will cure rickets or prevent its development, but it is important to remember that exposure in the wintertime for the greater part of the day is insufficient to accomplish this. In other words, sunlight can only be relied upon for protection against rickets in the summertime and it ought not be relied on for the cure of rickets since other more efficient means are so readily available.

Rickets can be cured with either the mercury vapor quartz lamp or the carbon arc lamp. The plan of treatment with either lamp is roughly as follows: The lamp is placed at a distance of 2 to 3 feet from the body (a greater distance is allowable in the case of the carbon arc lamp), and exposures of both front and back are carried out either at alternate sessions or at each session. The first total exposure is for one minute, the second for two minutes, and each subsequent one is increased by one minute until a total of ten minutes is reached. To cure rickets this treatment must be continued for at least a month, at the end of which time it can be reduced. To prevent rickets the radiations may be carried out every other day and the session limited to five minutes. The only real danger in the use of the ultraviolet radiation for the cure of rickets is when the subjects are blonds and have poorly pigmented skins. In the case of blonds it is advisable to resort to other forms of treatment.

RICKETS OF ENDOGENOUS ORIGIN

It is necessary to point out with the greatest emphasis that rickets is not always due to a deficiency in vitamin D but may result from disturbances in metabolism which cause depletions of the calcium and phosphorus of the body to such an extent that rickets becomes the inevitable result. So far as is known at present all of these forms of rickets of endogenous origin depend in the last analysis on disturbances in renal function.

One of these, the de Toni-Fanconi disease complex, is characterized by the development of rickets of the low phosphorus variety, histologically indistinguishable from rickets due to deficiency in vitamin D, by renal diabetes, and by the excretion of great quantities of amino acids in the urine.

Rickets may be associated with disturbances in cystine metabolism. It is not at present clear whether this is a distinct metabolic form of rickets or whether it belongs to the de Toni-Fanconi disease complex with, as a characteristic feature, the presence of cystine deposits in the tissues.

Nephrocalcinosis with rickets and dwarfism was first described by Butler and Albright.[3, 4] The striking feature is rickets of the low phosphorus variety associated with chloride acidosis and, as a development, deposition of calcium-phosphate in the kidney, sometimes in enormous amount, visible in the X-ray film. The acidosis is due to a retention of chlorides. The kidney has a diminished ability to produce ammonia and to conserve base. For the description of these forms of rickets of endogenous origin, the reader is referred to the literature.[1]

RICKETS REFRACTORY TO VITAMIN D

Before concluding, it is necessary to point out that a form of rickets is not very infrequently encountered, particularly in the large clinics, in which the sole peculiarity is refractoriness to vitamin D therapy. In these cases the various forms of metabolic rickets must be excluded, and the final proof is obtained by therapeutic failure of ordinary vitamin D treatment but success with large doses. Though children suffering from this kind of rickets do not react to ordinary dosages of vitamin D, they will react to very large doses. In a case of Albright's[2] in an adult the dose was worked up to 1,500,000 I.U. before a decisive therapeutic effect was obtained. In the case of children, it is often necessary to raise the dosage by steps to as high as 150,000 to 200,000 I.U. of vitamin D daily. For the discussion of this condition in which the essential trouble seems to lie in the failure of vitamin D to act on the mechanisms involved in calcification, the reader is referred to the literature.

BIBLIOGRAPHY

1. Albright, F. *Medicine* 25:399, 1946.
2. Albright, F., Butler, A. M., and Bloomberg, E. *Am. J. Dis. Child.* 54:529, 1937.
3. Albright, F., et al. *Bull. Johns Hopkins Hosp.* 66:7, 1940.
4. Butler, A. M., Wilson, J. L., and Farber, S. *J. Pediat.* 8:489, 1936.
5. Follis, R. H., Jackson, D., Park, E. A. *Am. J. Dis. Child.* 60:745, 1940.
6. Follis, R. H., Jackson, D., Eliot, M., Park, E. A. *Am. J. Dis. Child.* 66:9, 1943.
7. Freudenberg, E. *Ann. Paediat.* 161:338.
8. Hamilton, B., and Dewar, M. M. *Am. J. Dis. Child.* 54:548, 1937.
9. Harrison, H. E., and Harrison, H. C. *J. Clin. Invest.* 20:47, 1941.
10. Howland, J., and Kramer, B. *Am. J. Dis. Child.* 22:105, 1921.
11. Howland, J., and Kramer, B. *Tr. Am. Pediat. Soc.* 34:204, 1922.
12. Iversen, P., and Lenstrup, E. *Forthandlingserne ved Forste Nordiske Kongress für Pediatri,* 1920.
13. Jeans, P. C., and Stearns, G. *J.A.M.A.* 111:703, 1938.
14. Jeans, P. C., and Stearns, G. *J. Pediat.* 13:730, 1938.
15. Kassowitz, M. Rachitis, Vienna, Wilhelm Braumüller, 1882; *Wien. med. Presse,* 38:97, 139, 1897.
16. Shohl, A. T. *J. Nutrition* 14:69, 1937.
17. Speidil, T. D., and Stearns, G. *J. Pediat.* 17:506, 1940.
18. Stearns, G., Jeans, P. C., and Vandecar, V. *J. Pediat.* 9:1, 1936.
19. Tisdall, F. F., and Brown, A. *Am. J. Dis. Child.*, 34:721, 737, 742, 1927; 36:734, 1928; 42:1144, 1931; *J.A.M.A.* 92:860, 1929.
20. Trousseau, A. Rickets. Philadelphia, Lindsay and Blackiston, 1873.
21. Vollmer, H. *Ztschr. f. Kinderh.* 45:265, 1928.
22. Wieland, E. *Virchows Arch. f. path. Anat.* 197:167, 1909.

Chapter 17

VITAMIN K MALNUTRITION*

E. D. Warner

VITAMIN K is a term applied to a group of quinone compounds which have antihemorrhagic properties. The term is applied not only to the naturally occurring compounds but also to a large group of synthetic quinone compounds which have similar biologic activity with respect to the blood clotting mechanism.

The existence of an antihemorrhagic food factor was first suspected in 1929[16] when it was noted that young chicks which were maintained on a low-fat diet frequently developed a fatal tendency to bleed and that the hemorrhagic tendency could not be prevented by the administration of vitamin C. This observation led to the discovery of a previously unrecognized antihemorrhagic food factor[3, 4, 17, 18] which was fat-soluble. The new vitamin was designated vitamin K after the Danish word *Koagulations vitamine*. It was found to be widely distributed in natural foodstuffs, being especially abundant in alfalfa and similar green plants, and to be produced by a variety of bacteria.[2]

The application of the newly recognized vitamin to human therapy followed logically from work done in widely scattered laboratories. It was found that the bleeding tendency associated with vitamin K deficiency in chicks,[29] obstructive jaundice in man,[27] biliary fistula in dogs,[22] and hemorrhagic disease of the newborn,[10, 41] is due to deficiency of prothrombin in the blood plasma. The dramatic curative effect of vitamin K on the hemorrhagic tendency associated with obstructive jaundice was demonstrated in 1938[12, 21, 38] and on the hypoprothrombinemia of the newborn in 1939.[34] Numerous publications in recent years have confirmed the correctness of these studies.

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CHEMISTRY AND PHYSIOLOGY

Attempts to isolate the vitamin and to determine its chemical nature met with considerable success[1, 18, 19] even before the discovery of its application to human disease. With the discovery of its application to man, the new vitamin became the subject of more widespread investigation and isolation of the vitamin was accomplished almost simultaneously in two different laboratories[8, 20, 24] in 1939. The more potent naturally occurring vitamin K_1, obtained from alfalfa meal, was found[24, 25] to be 2-methyl-3-phytyl-1,4-naphthoquinone; a less potent vitamin K_2, isolated from putrefied sardine meal, was identified as 2-methyl-1,4-naphthoquinone with a C_{30} side chain in the third position. The discovery[7] that 2-methyl-1,4-naphthoquinone was highly active as vitamin K in animals led to the discovery that many related quinones, especially modifications of 2-methyl-1,4-naphthoquinone and of 2 methyl-1,4-naphthohydroquinone, are highly active as vitamin K. The parent material of the most active substance apparently is 2-methyl-naphthalene, the most favorable form being 1,4-naphthoquinone with a methyl group in the second position.

The vitamin K compounds which occur in nature and many of the related compounds prepared synthetically are relatively insoluble in water. For this reason they are not convenient forms of the vitamin for therapeutic use, especially if parenteral administration is desired. However, a number of highly active compounds have been synthesized, especially modifications of 2-methyl-1,4-naphthohydroquinone, which are readily soluble in water. Several of these are available in sterile form suitable for parenteral administration. In an attempt to standardize the somewhat confused nomenclature of vitamin K preparations, the Committee on Nomenclature of the American Medical Association[23] has adopted the term "menadione" and has authorized its use as a nonproprietary name to describe the substance 2-methyl-1,4-naphthoquinone. Thus vitamin K_1 may be designated as phytyl-menadione, and 2-methyl-1,4-naphthohydroquinone becomes menadiol.

Determination of the antihemorrhagic activity of the vitamin K compounds is dependent upon bio-assay. Such bio-assay is based upon the effect of the vitamin on the concentration of prothrombin in the blood when sources of vitamin K other than the test material are eliminated. Both curative and preventive methods of assay have been used extensively and several different units of antihemorrhagic activity have been described. These units vary widely, depending upon the particular conditions of the tests used by the various workers.[6] The present tendency is to use menadione as the reference standard and to express the activity of other compounds in terms of a specified amount of menadione.

Physiologically, vitamin K is essential for the maintenance of prothrombin in the blood plasma. The prothrombin, a part of the plasma protein complex, apparently is produced in the liver. If the liver is removed[36, 40] or is severely damaged,[37] the concentration of prothrombin in the blood decreases. In the absence of vitamin K, the prothrombin level falls even though the liver is intact. Very little is known about the mechanism by which the vitamin is used in the fabrication of prothrombin. Purified prothrombin does not contain the quinones, nor does prothrombin have vitamin K activity. Moreover, only minute amounts of the vitamin are required. Thus, it does not appear likely that vitamin K, as such, forms a substantial part of the prothrombin molecule.

The amount of vitamin K required to supply daily needs in man is not known accurately. Controlled experiments with laboratory animals and with normal newborn human infants indicate that the daily requirement of man probably is not more than a fraction of a milligram of 2-methyl-1,-4-naphthoquinone. However, there is some evidence that doses which are many times the daily requirement will effect a more prompt prothrombin response than is obtained with small doses. Experience indicates that both the naturally occurring and the synthetic vitamin K compounds have very low toxicity. For this reason it is safe to administer relatively large doses.

Under natural conditions the animal has two sources of vitamin K. Vitamin K_1 is ingested with the food. This compound is distributed widely in nature and even a diet otherwise very inadequate will usually contain more than the minimal requirements of vitamin K. A second source of vitamin K is presumably supplied by the bacterial flora in the intestinal tract. Many bacteria, including members of the normal intestinal flora, produce vitamin K_2. These naturally occurring compounds are fat-soluble and are absorbed from the intestine with the aid of bile salts. After absorption, some of the vitamin is utilized in the production of prothrombin, presumably by the liver. If an excessive amount is absorbed, some of it is stored in the body. The site of storage is not known. Most of the excess is rapidly lost or destroyed. For this reason any stores which may exist are rapidly depleted unless the intake is continued.

ETIOLOGY OF VITAMIN K DEFICIENCY

The most obvious cause of vitamin K deficiency in man is dietary. This was the basis of the hemorrhagic chick disease which led to the discovery of the vitamin. In the mammal, elimination of the vitamin from the diet does not usually result in hemorrhagic disease. Apparently the vitamin K_2 produced by the bacteria in the bowel is sufficient to prevent a severe deficiency from developing in most instances. The newborn human infant is an exception to this general rule. Very little vitamin K is transferred to the fetus from the maternal sources as stores under the conditions of normal diet during pregnancy. At the time of birth, the bacterial flora is not yet established in the intestinal tract. The supplemental diet commonly given the infant during the first few days of life contains very little vitamin K. As a result, some degree of vitamin K deficiency due simply to inadequate intake is the rule during the first few days of extra-uterine life. In most infants the hypoprothrombinemia is not sufficiently severe for spontaneous hemorrhages to occur. Rarely, the prothrombin falls to a very low level and serious bleeding may occur.

A second mechanism for the development of a vitamin K deficiency in man, and the most frequent cause in severe cases, is faulty absorption of the vitamin from the intestine. The commonest cause of defective absorption of vitamin K from the intestine is the absence of bile salts to aid in the absorption of fats. If the common bile duct is obstructed so that bile does not reach the intestine, or if a fistula drains the bile to the outside, vitamin K, along with other fat-soluble substances, will be absorbed very poorly. For this reason, serious vitamin K deficiency is a common complication of biliary tract disease. The seriousness of the condition is often aggravated by the fact that the biliary tract disease demands surgery and any tendency to bleed is a special concern when an operation is necessary.

Any condition which seriously interferes with intestinal absorption may be a cause of vitamin K deficiency. Thus, a tendency to bleed resulting from vitamin K deficiency may be encountered in persons with severe and protracted diarrhea, celiac syndrome, fistulas which short-circuit large portions of the bowel, and operative removal of large segments of the intestinal tract. However, the amount of the vitamin which is necessary to maintain the plasma prothrombin above a critical level is very small. For this reason, a significant tendency to bleed is not common even though there is considerable impairment of intestinal absorption, unless bile salts are absent in the bowel.

A possible contributing factor in the hemorrhagic diathesis due to faulty absorption of vitamin K is impairment of liver function. Either vitamin K deficiency or impaired liver function will produce hypoprothrombinemia, and when both factors are present the effect upon the prothrombin level of the blood is additive. Some degree of functional impairment of the liver is common in cases of long-standing biliary tract disease. Fortunately, the vitamin K deficiency can be corrected promptly by the administration of the vitamin, and the degree of impairment of liver function alone is not sufficient in most cases to cause a severe hypoprothrombinemia. There is some evidence that hypoprothrombinemia due to impaired liver function will respond to massive doses of vitamin K.[32, 33] However, work with experimental animals indicates little or no effect of vitamin K on hypoprothrombinemia due to experimental liver injury.[5, 9, 11] In fact, the failure of hypoprothrombinemia to respond to vitamin K has been advocated as an index of liver damage.

LABORATORY FINDINGS

The only manifestation of vitamin K deficiency is a hemorrhagic diathesis due to hypoprothrombinemia which will respond to administration of the vitamin. The normal prothrombin level is considerably higher than that required to prevent any detectable bleeding tendency. For this reason, vitamin K deficiency does not become manifest until the plasma prothrombin has fallen to less than half the normal concentration. Usually there is no significant tendency to bleed until the prothrombin level has been reduced to less than one-third of the normal level. Simple whole-blood clotting time (whether capillary or venous blood) and the standard bleeding time tests are therefore of little value for the clinical detection of impending hemorrhage from vitamin K deficiency. To detect a deficiency before hemorrhage occurs, it is important to recognize the type of person in whom such a deficiency is likely, and to determine the prothrombin level in the blood. This is especially important in patients in whom some operative procedure is indicated. In cases of vitamin K deficiency, surgery is often followed by a very rapid fall in the prothrombin level, and postoperative oozing is a real danger even though there was only moderate hypoprothrombinemia prior to the operation.

Since the detection of vitamin K deficiency is dependent upon the finding of a hypoprothrombinemia which can be corrected by specific therapy, the significant laboratory test is the determination of the concentration of prothrombin in the plasma. The methods available for determining the prothrombin concentration in the blood are indirect and depend upon measuring the biologic activity of the prothrombin in the blood-clotting process.

In the classical concept of clotting, the process occurs in two stages:

1. Prothrombin + thromboplastin + calcium $\longrightarrow$ thrombin
2. Thrombin + fibrinogen $\longrightarrow$ fibrin clot

In the first stage, the prothrombin is converted into the active clotting agent, thrombin. In the second stage, thrombin acts upon the fibrinogen to convert it into the fibrin clot. Each of these stages requires time. In the second stage, the time required is dependent upon the amount of thrombin present. Within wide limits, a very small amount of thrombin eventually will convert all of the fibrinogen present into fibrin. With a large amount of thrombin the clot forms more rapidly. Thus, under standard conditions the speed of the second stage of clotting can be used as a measure of the amount of thrombin present. The two-stage prothrombin method of Warner, Brinkhous, and Smith[37] separates the two stages of the clotting process and converts all of the prothrombin present into thrombin as a preliminary step. The amount of thrombin formed, then, is measured in terms of the speed of the second stage of the clotting process. A number of modifications of the two-stage method have been described. The two-stage methods have the advantage of making it possible to standardize the conditions under which the reaction takes place and to avoid error due to the influence of factors which may retard or accelerate the speed of the first phase. It is known that factors such as *p*H, electrolyte concentration, and colloidal state of the mixture influence the speed of this reaction. There are also differences in the rate of conversion of the prothrombin in plasma. This is especially conspicuous in differences between various species of animals,[39] but there is good evidence that the conversion rate of prothrombin in man varies under certain conditions. Recent work[26, 35] indicates that a conversion factor, normally present in the plasma, may greatly alter the speed of the first stage of clotting even though the amount of prothrombin remains constant.

A second type of method is usually referred to in the literature as a one-stage prothrombin method or a method for determining the prothrombin time. This method is in reality an accelerated clotting time obtained by adding an excess of thromboplastin to the blood. When blood is allowed to clot, most of the time required is used for the conversion of prothrombin into the active form, thrombin, in the first stage of the clotting process. The most significant factor in determining the amount of time required for this conversion is the amount of thromboplastin present. If a large excess of thromboplastin is added artificially, however, the prothrombin conversion time becomes dependent mainly upon the amount of prothrombin present. Under these conditions the total clotting time, mainly prothrombin conversion time, can be used as a measure of the amount of prothrombin present in the blood plasma. This is the basis of Quick's[27] method and of all the other one-stage methods that have been described. Since the original description, many modifications have been devised for measuring the prothrombin time. These methods have the disadvantage that factors which modify the prothrombin conversion time, other than the amount of prothrombin, are not controlled. On the other hand, the one-stage methods have the great advantage of simplicity and they do provide a very practical measure of the activity of the prothrombin in the clotting process. Any of the methods of this type, when properly controlled with parallel determinations on normal blood, appears to be satisfactory for practical clinical work. The one-stage methods which utilize fresh whole blood are the simplest. By eliminating the need for recalcification of the blood, these methods avoid errors that may result from the addition of improper amounts of calcium. However, the sensitivity of the one-stage methods to minor variations in prothrombin concentration is increased if the blood is diluted.[14] For this reason the use of decalcified plasma rather than freshly drawn whole blood is sometimes desirable.

Probably the simplest practical test of prothrombin activity for clinical use is that described as the "bedside" test.[44] This method is so simple that it can be performed literally at the bedside and does not require an experienced technician.

To perform the test, place 0.1 cc. of thromboplastin solution in a small test tube which is graduated at 1.0 cc. Draw 1 to 2 cc. of venous blood and add 0.9 cc. of the freshly drawn blood to the thromboplastin in the tube. Invert the tube to mix the blood with the thromboplastin solution, and note the time required for the mixture to clot. The end-point is easily determined by tilting the tube every few seconds. The time measured is the interval from the time the blood is added to the thromboplastin until a definite clot forms. This accelerated clotting time is compared with that obtained with a similar sample of normal blood. The prothrombin activity can then be expressed as a percentage of normal by the simple calculation:

$$\frac{\text{clotting time of control (sec.)}}{\text{clotting time of unknown (sec.)}} \times 100 = \begin{array}{l}\text{prothrombin activity}\\ \text{in per cent of normal.}\end{array}$$

The results obtained with this test in vitamin K deficiency are quite similar to those obtained with the more complicated tests of the one-stage type. The only precautions needed for consistently good results are easily met. It is important that the syringe be clean and dry and that the blood be obtained by a clean venepuncture. Contamination of the blood with large amounts of tissue juice, which may occur if difficulty is encountered in entering the vein, may shorten the clotting time and lead to a significant error. The needle should be removed from the syringe before transferring the blood to the test tube, to avoid foaming or undue trauma to the cellular elements.

At times it is difficult to obtain even 1.0 cc. of venous blood for prothrombin determination. This is especially true in dealing with infants. Several micromodifications of the one-stage type test which can be carried out with a single drop of blood have been described.

A micromodification[42] of the "bedside" test is performed with a drop of fresh capillary blood obtained from a small stab wound. The first drop of blood is wiped away to avoid contamination with an excessive amount of tissue juice. With the aid of a micropipette, 25 cu. mm. of blood is then quickly drawn and added to 5 cu. mm. of thromboplastin solution previously placed upon a clean glass slide. The blood and thromboplastin are mixed by stirring with a small glass rod and the clotting time noted.

The results obtained with this microadaptation of the "bedside" method are quite satisfactory for clinical use. With the small amount of blood used for the test, chilling of the blood quickly occurs and the clotting time is slightly longer than that obtained with the test tube method. For this reason, it is important that the determinations on the unknown and control bloods be made at the same room temperature.

The only reagent needed for the "bedside" prothrombin method is thromboplastin. A number of thromboplastin preparations are available commercially. Any of these appear to give satisfactory results, provided the activity of the thromboplastin solution is sufficient to give a clotting time with normal blood no greater than forty seconds.

Certain discrepancies between the results obtained with the one-stage type of prothrombin method and those obtained with two-stage methods are important, especially when dealing with young infants. The absolute quantity of prothrombin, as determined by the two-stage methods, is physiologically less in the newborn of any species, including man, than in the adult.[10] In man, the concentration of prothrombin in the blood at birth is only 30 per cent to 50 per cent of the adult level. Under normal conditions the concentration gradually increases, but the adult level is not reached until the second half of the first year of life. Some compensatory mechanism in the infant, not yet fully understood, results in an increased speed of conversion of the prothrombin to thrombin so that the clotting time of the infant's blood is not prolonged, and under normal conditions there is no tendency to bleed.[43] When measured by the one-stage prothrombin methods, the activity of the prothrombin is found to be within normal limits, whereas with the two-stage methods the concentration of prothrombin is found to be considerably below the adult level. A similar discrepancy between the results obtained with the two-stage and one-stage methods is encountered in certain cases of mild chronic liver disease. Differences in clotting time and in prothrombin time between different species are explainable, in part, on the basis of differences in the rate of conversion of the prothrombin rather than on the absolute concentration of the prothrombin in the blood.[39] For this reason, the one-stage tests, which measure the activity rather than the actual amount of the prothrombin present, may give misleading results in certain types of research work. In clinical work, however, the one-stage tests do measure the activity of the prothrombin in the clotting process. This provides a practical measure of the capacity of the blood to clot. The one-stage tests are dependable for detection of hypoprothrombinemia, from any cause, which is of sufficient degree to cause a hemorrhagic diathesis, and they have proved satisfactory for the control of vitamin K therapy.

DIAGNOSIS

The diagnosis of vitamin K deficiency prior to the actual onset of bleeding depends upon suspecting it from the condition of the patient and demonstrating hypoprothrombinemia which responds to administration of the vitamin. If the hypoprothrombinemia is due to severe impairment of liver function or is the rare congenital type, or if it is an apparent hypoprothrombinemia due to deficiency of the "conversion factor," vitamin K will not induce the expected response. If there is actual bleeding, vitamin K deficiency is readily distinguished from cases in which hypoprothrombinemia is not the cause of the bleeding by determining the prothrombin concentration in the blood. Thus, such conditions as hemophilia, the purpuras, scurvy, and heparin-induced inhibition of clotting are associated with normal prothrombin values, and vitamin K is not effective in correcting the bleeding tendency in these conditions.

As encountered in nature, hypoprothrombinemia of significant degree usually is the result of liver damage or vitamin K deficiency, or both. However, hypoprothrombinemia from other causes is encountered occasionally. In rare instances there appears to be a congenital hypoprothrombinemia in an otherwise normal individual. Hypoprothrombinemia of this type does not respond to vitamin K therapy.[28]

Dicumarol, the active principle of "toxic hay" responsible for "toxic sweet clover disease," produces a profound depression of the prothrombin level.[13] This drug is becoming increasingly popular as a therapeutic agent for lowering the clotting power of the blood in certain cases of thromboembolic disease. The mechanism by which dicumarol produces hypoprothrombinemia is not understood. Vitamin K is only partially effective in correcting hypoprothrombinemia of this origin and massive doses are required.[15] Hypoprothrombinemia of a significant degree has been reported as occurring at times in patients receiving salicylates,[30] especially if administration of large doses is continued over a considerable period of time. The mechanism by which the hypoprothrombinemia is produced is not understood and, as in the case of dicumarol, the protective action of vitamin K is at best limited.

The problem of vitamin K deficiency in the newborn is of special interest because of its common occurrence and the lack of general agreement regarding the therapeutic role of prophylactic administration of vitamin K to the mother during labor or to the infant after birth. Although some degree of vitamin K deficiency is the rule in the neonatal period, the decrease in blood prothrombin is not sufficiently extreme for a bleeding tendency to develop in most infants. In an occasional infant, hypoprothrombinemia becomes severe and hemorrhagic disease of the newborn results. The discovery of vitamin K and the demonstration of its efficacy in correcting the bleeding tendency due to vitamin K deficiency have made possible a remarkably efficient method for treating hemorrhagic disease of the newborn. An increase in the prothrombin level and disappearance of the bleeding tendency become manifest in a matter of hours after the administration of vitamin K. It is important to emphasize in this connection that hemorrhagic disease of the newborn (hypoprothrombinemia hemorrhagica neonatorum) must not be confused with bleeding conditions which may occur in infants from causes other than vitamin K deficiency. Hemorrhagic disease of the newborn may be defined as a clinical entity, limited in its occurrence to the first week of postnatal life and characterized by a disturbance in blood coagulation specifically due to prothrombinopenia which, in turn, is due to a vitamin K deficiency. Other causes of hypoprothrombinemia, such as liver insufficiency, are unusual in the newborn, but possible. Vitamin K cannot be expected to correct any bleeding tendency which is due to causes other than deficiency of this vitamin. The gastrointestinal hemorrhages are commonly known as melena neonatorum and are usually associated with hypoprothrombinemia. Hemorrhage occurring in the central nervous system in the newborn is usually due to traumatic injury incident to birth and may or may not be associated with hypoprothrombinemia.

TREATMENT

The amount of vitamin K required to supply daily needs is very small, probably not more than a few micrograms. There is, however, abundant evidence that no harmful effects are produced by doses which are many times the minimum requirement. There is also some evidence that large doses will cause a more rapid rise in prothrombin than will smaller amounts of the vitamin. The potency of most commercially available vitamin K preparations is designated in terms of the antihemorrhagic activity of an equivalent amount of menadione. The commonly recommended dose of the equivalent of 1 to 5 mg. of menadione per day is an effective therapeutic dose for active treatment. Although greatly in excess of daily requirements, daily doses of this amount leave a wide margin of safety below any possible toxic effect.

The rapid progress in knowledge of vitamin K and its therapeutic effect upon the bleeding tendency due to vitamin K deficiency has resulted in the preparation of numerous forms of the vitamin which are suitable for therapeutic use. The oily preparations are best given orally. It is, of course, essential that bile salts be present in the intestine to ensure absorption of the fat-soluble preparations. This necessitates the administration, in certain cases, of a preparation of bile salts in conjunction with the oily vitamin K preparations. Several of the water-soluble compounds in sterile solution suitable for parenteral administration are commercially available. These may be administered either orally or parenterally. In case of emergency, the response is slightly more rapid if the vitamin is given intravenously and no untoward effects have been reported from the injection of massive doses of the water-soluble vitamin K compounds.

Only small amounts of the vitamin are stored when excessive amounts are given. It is therefore important that the prothrombin level be followed by repeated determinations during the period of therapy and for a few days after administration of the vitamin is discontinued. Any recurrence of the conditions which led to the development of vitamin K deficiency can be expected to reestablish the deficiency state within a few days.

For purposes of vitamin K therapy, patients can be divided into three groups: those with normal prothrombin concentration in the blood, those with hypoprothrombinemia but without active bleeding, and those having hypoprothrombinemia associated with active bleeding.

Patients with normal prothrombin values ordinarily do not require vitamin K therapy. Those with disorders which are likely to lead to vitamin K deficiency (see *Etiology*) should be given prophylactic therapy, however, if an operation is to be performed. This will prevent the precipitous fall in the blood prothrombin level which may occur in these patients. The vitamin can be given orally if the patient can take medication by mouth and the operation is to be delayed for several days. It is advisable to give 2 to 5 mg. of one of the synthetic preparations daily for two to five days prior to the operation. Unless a water-soluble preparation is used, it is advisable to give 2 to 4 Gm. of bile salts along with the vitamin to ensure absorption from the bowel. During the postoperative period, 1 to 2 mg. of one of the water-soluble preparations should be given parenterally every day or two until oral administration can be resumed. The latter should be continued until the danger of vitamin K deficiency is past. If vitamin K is not administered during several days before the operation, 1 to 2 mg. of one of the water-soluble compounds should be given intravenously preoperatively and the treatment outlined above may be followed postoperatively.

The patients with hypoprothrombinemia constitute a potential emergency even though no operation is planned. If the prothrombin level is more than 50 per cent of normal, the prophylactic treatment outlined above is satisfactory. If the prothrombin level is below 50 per cent of normal, bleeding may occur at any time. In such persons daily parenteral administration of 2 to 5 mg. of the vitamin is advisable until the prothrombin level is normal, after which prophylactic therapy may be continued as outlined above.

Patients having hypoprothrombinemia associated with active bleeding should be given 2 to 5 mg. of the vitamin by intravenous injection daily until the prothrombin approaches normal. If the bleeding is at all severe, blood transfusion in addition to vitamin K therapy usually is indicated. As in the other groups, prophylactic treatment as outlined above should be instituted as soon as the hypoprothrombinemia is corrected, and it should be continued until the danger of vitamin K deficiency is past.

Severe liver damage is not a contraindication to vitamin K therapy, and there is suggestive evidence that vitamin K may decrease the incidence of hemorrhage in patients with hypoprothrombinemia due to liver disease. For this reason it is recommended by many that energetic vitamin K therapy be given to patients with liver damage even though no effect on the prothrombin level is evident.

Soon after the demonstration of the etiologic relationship of vitamin K and hypoprothrombinemia in the newborn, it became apparent that the transient prothrombin deficiency might be controlled by administering vitamin K to the expectant mother.[31] A number of studies on the incidence of hemorrhage and on the infant mortality rate in the neonatal period suggested that a decrease in the incidence of both neonatal hemorrhagic manifestations and neonatal deaths resulted from the prophylactic administration of vitamin K. Evidence regarding possible reduction in the incidence of intracranial hemorrhage at the time of birth is less definite at the present time. Some statistical studies show no benefits from the prophylactic use of vitamin K. From the theoretical point of view it may be stated that a prothrombin deficiency is not manifest at the time of birth in the majority of infants. Hemorrhage at the time of delivery is usually the direct result of severe trauma and is not associated with a hemorrhagic diathesis as a contributing cause. In an occasional infant, however, hypoprothrombinemia is present at the time of birth. It is logical to assume that the prophylactic administration of vitamin K would decrease the incidence and extent of intracranial hemorrhage at the time of birth in these infants. Also, the administration of vitamin K may be expected to decrease the danger of late bleeding into the injured areas during the first few postnatal days.

The question of the amount of benefit that may be expected in infant mortality and morbidity from the prophylactic administration of vitamin K to expectant mothers, or to newborn normal infants, will remain a subject of debate until the results of more extensive statistical studies become available. This is particularly true with regard to possible late effects from sublethal intracranial hemorrhage. There is general agreement that vitamin K should be administered to the infant whenever a tendency to bleed becomes evident and that the routine administration of vitamin K to either the expectant mother or the newborn infant has no untoward effects.

Commonly recommended procedures to prevent complications from vitamin K deficiency in the newborn are the following: (1) administration of vitamin K, as outlined above for prophylactic treatment, to the mother during the last week of pregnancy; or (2) administration of 2 mg. of one of the water-soluble preparations to the mother by intravenous injection between six and twenty-four hours prior to delivery; or (3) administration of 2 mg. of a water-soluble vitamin K compound to the infant by parenteral injection immediately after birth. Parenteral injection is recommended prior to any operation to be performed on the infant during the neonatal period.

BIBLIOGRAPHY

1. Almquist, H. J. Purification of the antihemorrhagic vitamin by distillation. *J. Biol. Chem.* 115:589, 1936.
2. Almquist, H. J., Pentler, C. F., and Mecchi, E. Synthesis of the antihemorrhagic vitamin by bacteria. *Proc. Soc. Exper. Biol. & Med.* 38:336, 1938.
3. Almquist, H. J., and Stokstad, E. L. R. Dietary hemorrhagic disease in chicks. *Nature*, London 136:31, 1935.
4. Almquist, H. J., and Stokstad, E. L. R. Hemorrhagic chick disease of dietary origin. *J. Biol. Chem.* 111:105, 1935.
5. Andrus, W. DeW., Lord, J. W., and Moore, R. A. The effect of hepatectomy on the plasma prothrombin and the utilization of vitamin K. *Surgery* 6:899, 1939.

6. Ansbacher, S. The bioassay of vitamin K. *J. Nutrition* 21:1, 1941.
7. Ansbacher, S., and Fernholz, E. Simple compounds with vitamin K activity. *J. Am. Chem. Soc.* 61:1924, 1939.
8. Binkley, S. B., MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A. Isolation of vitamin K_1 *J. Biol. Chem.* 130:219, 1939.
9. Bollman, J. L., Butt, H. R., and Snell, A. M. The influence of the liver on the utilization of vitamin K. *J.A.M.A.* 115:1087, 1940.
10. Brinkhous, K. M., Smith, H. P., and Warner, E. D. Plasma prothrombin level in normal infancy and in hemorrhagic disease of the newborn. *Am. J. M. Sc.* 193:475, 1937.
11. Brinkhous, K. M., and Warner, E. D. Effect of vitamin K on hypoprothrombinemia of experimental liver injury. *Proc. Soc. Exper. Biol. & Med.* 44:609, 1940.
12. Butt, H. R., Snell, A. M., and Osterberg, A. E. Use of vitamin K and bile in treatment of the hemorrhagic diathesis in cases of jaundice. *Proc. Staff Meet, Mayo Clinic* 13:74, 1938.
13. Campbell, H. A., and Link, P. K. Studies on the hemorrhagic sweet clover disease: IV., The isolation and crystallization of the hemorrhagic agent. *J. Biol. Chem.* 138:21, 1941.
14. Campbell, H. A., Smith, W. K., Roberts, W. L., and Link, K. P. Studies on the hemorrhagic sweet clover disease: II., The bioassay of hemorrhagic concentrates by following the prothrombin level in the plasma. *J. Biol. Chem.* 138:1, 1941.
15. Cromer, H. E., Jr., and Barker, N. W. Effect of large doses of menadione disulfite (synthetic vitamin K) on excessive hypoprothrombinemia induced by dicumarol. *Proc. Staff. Meet. Mayo Clinic* 19:217, 1944.
16. Dam, H. Cholesterinstoffwechsel in Hühneiern and Hühnchen. *Biochem. Ztschr.* 215:475, 1929.
17. Dam, H. Hemorrhages in chicks reared on artificial diets: A new deficiency disease. *Nature,* London 133:909, 1934.
18. Dam, H. Antihaemorrhagic vitamin of the chick, occurrence and chemical nature. *Nature,* London 135:652, 1935.
19. Dam, H. Antihaemorrhagic vitamin of the chick. *Biochem. J.* 29:1273, 1935.
20. Dam, H., Geiger, A., Glavind, J., Karrer, P., Karrer, W., Rothschild, E., and Salomon, H. Isolierung des Vitamins K in hochgereinigter Form. *Helvet chim. acta.* 22:310, 1939.
21. Dam, H., and Glavind, J. Vitamin K in human pathology. *Lancet* 1:720, 1938.
22. Hawkins, W. B., and Brinkhous, K. M. Prothrombin deficiency the cause of bleeding in bile fistula dogs. *J. Exper. Med.* 63:795, 1936.
23. *J.A.M.A.* 116:1054, 1941.
24. McKee, R. W., Binkley, S. B., MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A. Isolation of vitamins K_1 and K_2. *J. Am. Chem. Soc.* 61:1295, 1939.

25. McKee, R. W., Binkley, S. B., Thayer, S. A., MacCorquodale, D. W., and Doisy, E. A. Isolation of vitamin K_2 *J. Biol. Chem.* 131:327, 1939.
26. Owren, P. A. The coagulation of blood: Investigations on a new clotting factor. Oslo, 1947.
27. Quick, A. J. Prothrombin in hemophilia and in obstructive jaundice. *J. Biol. Chem.* 109:73, 1935.
28. Quick, A. J. Effect of synthetic vitamin K and of quinine sulfate on the prothrombin level. *J. Lab. & Clin. Med.* 31:79, 1946.
29. Schnøheyder, F. The quantitative determination of vitamin K. *Biochem. J.* 30:890, 1936.
30. Shapiro, S. Effect of synthetic vitamin K (menadione) on prothrombinopenia induced by salicylates in man. *J.A.M.A.* 125:546, 1944.
31. Shettles, L. B., Delfs, E., and Hellman, L. M. Factors influencing plasma prothrombin in the newborn infant: II., Antepartum and neonatal ingestion of vitamin K concentrate. *Bull. Johns Hopkins Hosp.* 65:419, 1939.
32. Snell, A. M. Vitamin K: Its properties, distribution and clinical importance. *J.A.M.A.* 112:1457, 1939.
33. Stewart, J. D., Rourke, G. M., and Allen, A. W. Control of postoperative bleeding in obstructive jaundice. *Ann. Surg.* 110:693, 1939.
34. Waddell, W. W., and Guerry, D. Effect of vitamin K on the clotting time of the prothrombin and the blood with special reference to unnatural bleeding of the newly born. *J.A.M.A.* 112:2259, 1939.
35. Ware, A. G., Guest, M. M., and Seegers, W. H. A factor in plasma which accelerates the activation of prothrombin. *J. Biol. Chem.* 169:231, 1947.
36. Warner, E. D. Plasma prothrombin: Effect of partial hepatectomy. *J. Exper. Med.* 68:831, 1938.
37. Warner, E. D., Brinkhous, K. M., and Smith, H. P. Quantitative study on blood clotting: Prothrombin fluctuations under experimental conditions. *Am. J. Physiol.* 114:667, 1936.
38. Warner, E. D., Brinkhous, K. M., and Smith, H. P. Bleeding tendency of obstructive jaundice: Prothrombin deficiency and dietary factors. *Proc. Soc. Exper. Biol. & Med.* 37:628, 1938.
39. Warner, E. D., Brinkhous, K. M., and Smith, H. P. Prothrombin conversion rate in various species. *Proc. Soc. Exper. Biol. & Med.* 40:197, 1939.
40. Warren, R., and Rhoads, J. E. Hepatic origin of the plasma-prothrombin: Observations after total hepatectomy in the dog. *Am. J. M. Sc.* 198:193, 1939.
41. Whipple, G. H. Hemorrhagic diseases: II., Antithrombin and prothrombin factors. *Arch. Int. Med.* 12:637, 1913.
42. Willumsen, H. C., Stadler, H. E., and Owen, C. A. Comparative effect of vitamin K and whole blood on prothrombin deficiency of newborn infant. *Proc. Soc. Exper. Biol. & Med.* 47:116, 1941.

43. Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P. Control of vitamin K Therapy: Compensatory mechanisms at low prothrombin levels. *Proc. Soc. Exper. Biol. & Med.* 40:595, 1939.

44. Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P. A simple bedside test for control of vitamin K therapy. *Am. J. Clin. Path.* Tech. Supp. IV, 13, 1940.

Chapter 18

THIAMINE MALNUTRITION

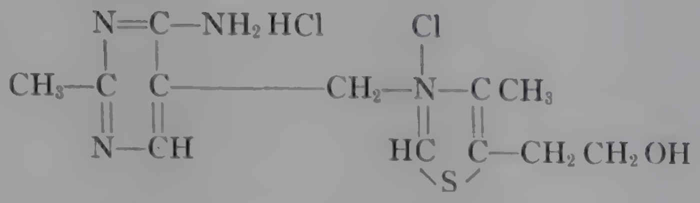
Ray D. Williams and Russell M. Wilder

Observations on thiamine deficiency had their inception in studies of antiberiberi factors in the latter half of the nineteenth century. The earliest were those of Takaki,[17] cited by Brandon,[2] on a disease of the legs. Eijkman[3] produced a disease of fowls which was like beriberi. Grijns[8] contributed the idea that beriberi was a deficiency disease. Funk[6, 7] in 1911 obtained material from rice polishings which cured beriberi. Jansen and Donath[11] first isolated a single substance from a natural source which had a curative effect upon beriberi. R. R. Williams and Cline[20] reported synthesis of thiamine in 1936.

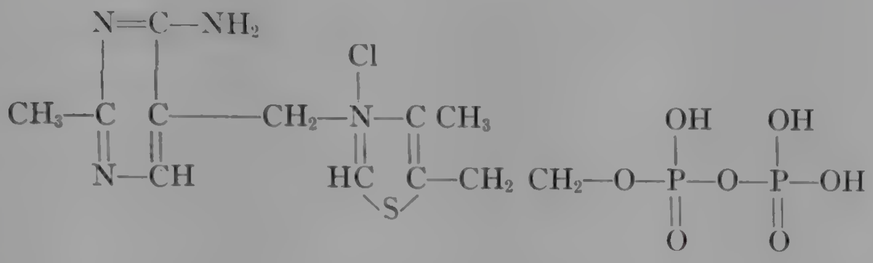
Observations of neuropathy with heart disease occurring spontaneously in the Orient and elsewhere were reported by Keefer[9] and Weiss.[19] The biochemical nature of beriberi was intensively studied by Platt and Lu.[15] These several observations on spontaneously occurring deficiency disease were landmarks in studies of nutrition, but it is not now believed that these investigators were studying a single vitamin deficiency. Controlled investigation of isolated thiamine deficiency in man is relatively recent.[4, 10, 12, 14, 20-23]

CHEMISTRY

The synthesis of thiamine, as reported by R. R. Williams and Cline[20] in 1936, represented the culmination of studies by them and other investigators in many countries and over many years on the chemistry of the so-called antiberiberi factor, vitamin B_1. The structural formula of thiamine hydrochloride is:



Löhman and Schuster in 1937 isolated from yeast a crystalline derivative of thiamine which had the structure of a pyrophosphoric ester. This so-called cocarboxylase has the following structure:



The pyrophosphoric ester of thiamine is the co-enzyme or prosthetic group of one or more enzymes which promote the utilization of pyruvic acid and related keto acids, which are normal intermediary products of carbohydrate metabolism. Both thiamine and the pyrophosphoric ester are relatively stable to heat if the medium is acid but are unstable to heat if the medium is alkaline. In an alkaline medium thiamine and its salts are easily oxidized and converted to a derivative, thiochrome, which fluoresces in ultraviolet light. This fluorescent property is used in the chemical analysis of biologic materials for thiamine.

PHYSIOLOGY

Investigations of animals deprived of thiamine revealed a disorder of carbohydrate metabolism. Pyruvic acid or related keto acids accumulated in the blood and tissues. The blood of a man in the normal basal state contains 0.7 to 1.0 mg. of pyruvic acid per 100 cc. Ingestion of food (for example, glucose) is associated with a rise of the value for pyruvic acid in one to two hours to levels of 1.25 to 1.5 mg. per 100 cc. Normally, the value returns to the basal figure in about three hours.

When a human being has been deprived of thiamine, administration of glucose either orally or parenterally is associated with abnormally high values for pyruvate and lactate in the blood; the metabolic abnormality becomes more severe as the thiamine deficiency progresses. The concentrations of the pyruvate and lactate in the blood normally rise after exercise, but in persons deprived of thiamine the values for pyruvate and lactate not only rise higher but also remain high for a much longer period of time than they do in persons adequately supplied with thiamine. The progressive nature of the metabolic disorder of pyruvate and lactate during restriction of thiamine in man is illustrated in Table 27.

It must be emphasized that pyruvic acid is one of the normal intermediary metabolites and that a function of thiamine is to assist the organism in using pyruvic acid in normal respiratory processes. Apparently the abnormal accumulation of pyruvate in states of thiamine deficiency reflects a general disturbance of tissue metabolism. The metabolism of pyruvate has been extensively reviewed by Stotz,[16] who stated that the principal avenues, namely, dismutation, oxidation, decarboxylation, and condensation, all appear to require diphosphothiamine (cocarboxylase). He added, however, that pantothenic acid and biotin in addition to thiamine are involved in the metabolism of pyruvate, although at which stage and by what mechanism are not yet clear. This last statement deserves emphasis, for it is apparent that other metabolic disorders such

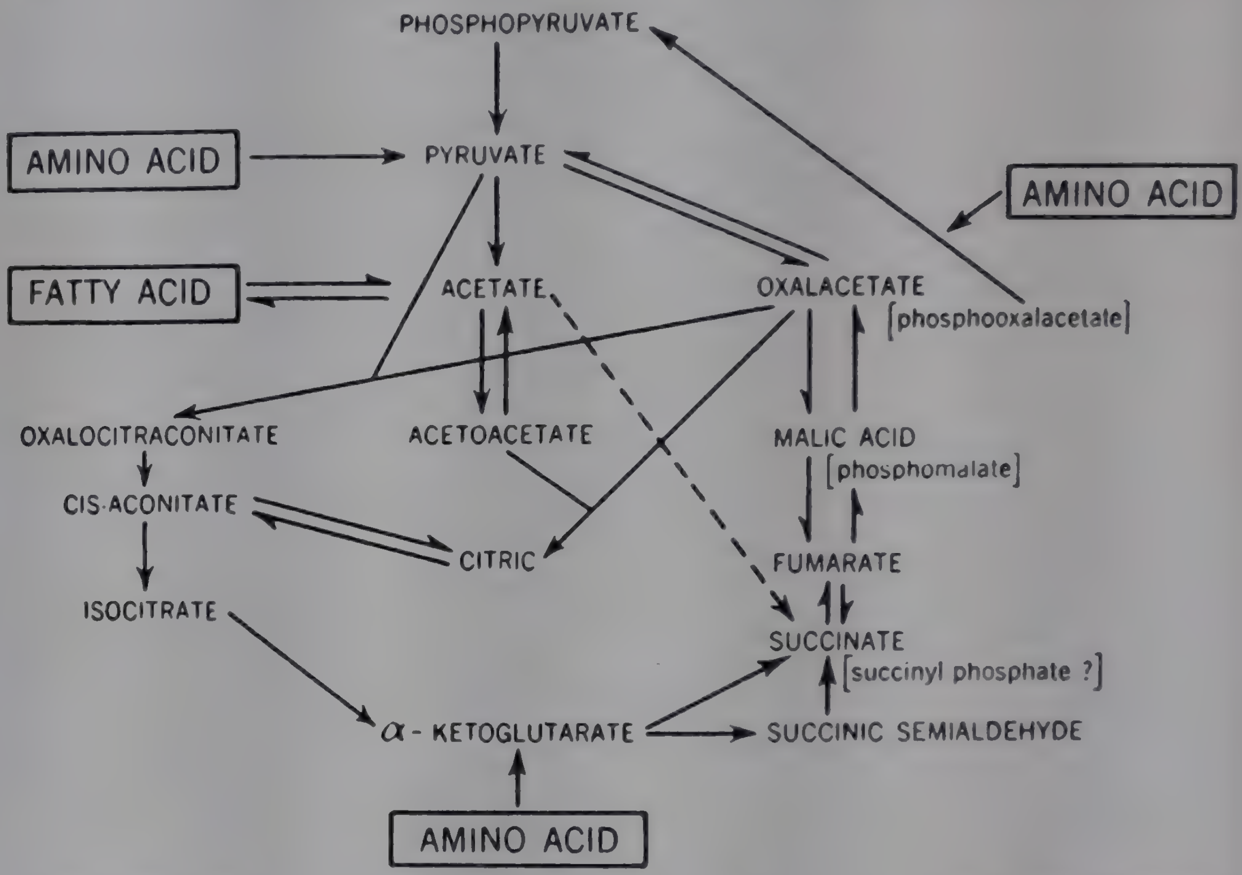

PHOSPHOPYRUVATE
AMINO ACID
PYRUVATE
AMINO ACID
FATTY ACID
ACETATE
OXALACETATE
[phosphooxalacetate]
OXALOCITRACONITATE
ACETOACETATE
MALIC ACID
[phosphomalate]
CIS-ACONITATE
CITRIC
FUMARATE
ISOCITRATE
SUCCINATE
[succinyl phosphate ?]
α - KETOGLUTARATE
SUCCINIC SEMIALDEHYDE
AMINO ACID

FIG. 24. The metabolic pool and relations with protein and fat. (From Stotz, Elmer: Pyruvate metabolism. In Nord, F. F., and Werkman, C. H.: Advances in Enzymology, and Related Subjects of Biochemistry. New York, Interscience Publishers, Inc., Vol. 5, p. 152 [fig. 2], 1945.)

TABLE 27. CONCENTRATION OF PYRUVIC ACID, LACTIC ACID, AND DEXTROSE IN THE BLOOD AFTER INTRAVENOUS ADMINISTRATION OF DEXTROSE AT INTERVALS DURING DEVELOPMENT OF THIAMINE DEFICIENCY*

Period of restriction of thiamine, (Days)	*Urinary excretion of thiamine in 24 hours, (Micrograms)*	*Urinary excretion of test dose of 1 mg. of thiamine hydrochloride in 4 hours, (Micrograms)*	*Clinical estimate of degree of deficiency State*†	*Concentration at given intervals after administration of dextrose, mg. per 100 cc. of blood*											
				Pyruvic acid				Lactic acid				Dextrose			
				Basal state	30 minutes	60 minutes	120 minutes	Basal state	30 minutes	60 minutes	120 minutes	Basal state	30 minutes	60 minutes	120 minutes
Subject 1: A woman aged 36, 168 cm. tall, weighing 56.5 kg.															
0	480	538	0	0.7	0.9	1.1	0.7	6.3	11.9	7.6	4.8	92	116	86	91
33	10	113	1	0.8	1.4	1.2	0.8	6.5	14.9	8.6	5.8	98	125	98	105
65	6	64	2	1.2	1.8	1.6	1.1	9.2	18.7	12.6	8.2	101	118	84	86
83	14	13	3	0.9	2.2	1.8	1.0	7.5	15.4	16.6	6.8	99	128	105	92
116	8	39	4	1.5	3.2	2.6	1.5	8.1	15.6	21.2	11.7	—	—	—	—
Subject 2: A woman aged 48, 161 cm. tall, weighing 55 kg.															
0	450	548	0	0.8	1.3	1.2	0.7	3.8	7.9	6.5	3.5	91	155	100	78
35	10	96	1	1.0	1.5	1.2	1.0	6.5	9.6	8.1	6.7	100	163	98	89
63	12	74	2	1.2	2.3	1.9	0.9	7.3	19.6	16.1	5.6	97	158	96	86
83	11	58	3	1.0	2.0	2.2	1.0	6.2	16.6	15.3	7.2	102	165	138	96
110	6	37	4	1.2	2.3	2.1	1.1	5.4	17.0	14.6	6.0	105	178	125	96

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* From WILLIAMS, R. D., MASON, H. L., POWER, M. H., and WILDER, R. M. Induced thiamine (vitamin B_1) deficiency in man; relation of depletion of thiamine to development of biochemical defect and of polyneuropathy. *Arch. Int. Med.* 71:38, 1943; (Table 1, page 44).

† 1, minimal state of thiamine deficiency; 2, moderately advanced state; 3, far advanced state, and 4, anatomic defect.

as diabetes mellitus, thyrotoxicosis, poisoning with heavy metals, and deficiencies of other vitamins may cause disturbances of tissue respiration which have an end effect on the cell much like that of thiamine deficiency. While these considerations do not lessen the emphasis on the role of thiamine in pyruvate metabolism, they indicate that thiamine is only one of several substances necessary for normal disposal of pyruvic acid. Of the many substances involved in intermediary metabolism, pyruvic acid is one of the most diverse in reaction. Barron[1] has pictured pyruvate as the "hub" toward which converge carbohydrate, fat, and protein in their catabolic and anabolic reactions. The relation of pyruvate to the "metabolic pool" is shown in Stotz's illustration (Fig. 24).

These general considerations indicate the over-all metabolic disarrangement in thiamine deficiency. Many metabolic processes are disturbed and many tissues of the body are impaired. Certain tissues are selectively affected in greater degree. Muscular tissues such as the striated muscles and the myocardium are impaired because of their high rates of energy exchange; nervous tissues suffer severely because they are inherently dependent on a menstruum of carbohydrate which, for the most part, is prepared by other tissues of the body.

PATHOLOGIC LESIONS OF THIAMINE DEFICIENCY

Pathologic lesions in induced thiamine deficiency in man have not been reported. Spontaneously occurring deficiency states attributed to thiamine deficiency (beriberi) have been described, but the effects of concomitant deficiencies of other nutrients and of intercurrent diseases cannot readily be excluded in such material. Descriptions of pathologic abnormalities in beriberi center about cardiac changes, degenerative changes of the nervous system, and the effects of anasarca. The heart, in beriberi, may be dilated and hypertrophied, its muscle fibers fragmented. The viscera may be congested. The changes in the central nervous system include degeneration of medullary sheaths and fragmentation of axis cylinders in tracts of the spinal cord, together with abnormalities of posterior spinal ganglia and anterior horn cells. The peripheral nerves, especially the sciatic and its branches, and in certain cases sympathetic ganglia, reveal degeneration. The muscles of the legs show atrophy, with loss of cross striation, shrunken sarcoplasm, and cloudy swelling or fatty infiltration. The anasarca of beriberi varies in degree and is not regularly associated with a blood plasma of lower than normal osmotic tension. It may possibly depend on abnormal permeability of capillaries.

Wintrobe was unable to produce neurologic lesions in pigs by restriction of thiamine[25] but did find such lesions after restriction of pantothenic acid and pyridoxine.[5] On the other hand, cardiac lesions of a lethal nature were observed. In spite of the failure of Wintrobe to induce abnormality of the nervous system by carefully conducted experiments on swine, it appears quite certain that thiamine deficiency in man has caused neurologic lesions. In man, when neurologic lesions interfere with physical activity the cardiovascular system is spared, whereas if activity is well maintained, symptoms and signs of cardiac failure supervene.

Preexisting cardiac disease such as coronary sclerosis, valvular lesions, and myocardial lesions due to other causes predisposes the heart to adverse effects from thiamine deficiency. It is also probable that generalized capillary vasodilatation and transudation of fluid add to the load on the myocardium and that this additional burden contributes to cardiac failure.

HUMAN REQUIREMENTS

The minimal requirement of thiamine for man ought in our opinion to be defined as the smallest amount of this vitamin necessary for performance of tissue respiration at normal rates in all parts of the body and under conditions of normal concentration of intermediary metabolites. If the intake of thiamine is less than this minimal amount, tissue respiration can continue under normal conditions only so long as stores of thiamine in the tissues are not severely depleted. It also is reasonable to assume that the biochemical reactions produced by cocarboxylase proceed more slowly when the stores of thiamine have become depleted and that depletion of these stores in itself represents an abnormality. In that case the minimal requirement should be that which is sufficient to prevent depletion of these stores.

In personal observations on induced thiamine deficiency in women on diets which represented about 2000 calories, an intake of 0.075 mg. of thiamine per 1000 calories was associated with an onset of extreme disability in thirty to sixty days; an intake of 0.175 mg. of thiamine per 1000 calories was associated with severe deficiency disease in ninety to one hundred and twenty days; an intake of 0.22 mg. of thiamine per 1000 calories did not prevent all evidence of deficiency of thiamine in several persons who were maintained on this intake for six to eight months. On the other hand, subjects on an intake of 0.45 mg. of thiamine per 1000 calories for a period of 243 days did not reveal any evidence of deficiency. In the study of Horwitt and associates[9] a total intake of 0.4 mg. of thiamine was shown to be below the minimal requirement of men who were relatively inactive and whose daily food consumption provided no more than 2000 calories. These observations and the observations of other investigators, especially those of Elsom and her co-workers[4] and Melnick,[14] are interpreted to indicate that the minimal requirement for thiamine is about 0.35 mg. per 1000 calories of a mixed diet and that a safe allowance of thiamine for man is about 0.5 mg. per 1000 calories.

Many circumstances may influence the minimal requirement of thiamine for man. Extensive experimental work with animals indicates that if the fat content of the diet is very high and provides a large proportion of the total calories, a smaller amount of thiamine is required than is necessary when the calories of the diet come predominantly from carbohydrate. Cowgill originally called attention to the desirability of considering requirement in terms of nonfat calories. The observations of Keys[10] on requirements of young men who consumed high caloric diets (3000 to 4000 calories per day) indicate that when the caloric intake is high, less thiamine per 1000 calories is needed. We interpret this to mean that 0.5 mg. of thiamine per 1000 calories is a safe allowance for the first 2000 calories of the diet and that less thiamine, perhaps only 0.1 to 0.2 mg. per 1000 calories, is necessary for metabolism of food above the 2000 calorie level.

Bacteria synthesize thiamine in the gastrointestinal tract, but it is not conclusively known that the thiamine thus synthesized is ordinarily available to the organism. The fact that human beings who were maintained under conditions of controlled thiamine intake did not obtain enough thiamine from the intestinal flora to prevent development of severe thiamine deficiency indicates that intestinal synthesis is not a dependable source of thiamine and that this factor need not be considered in recommendations of thiamine allowances for man.

Requirements for thiamine are increased in states of disease such as thyrotoxicosis, prolonged fever, and malignant disease, which elevate the metabolic rate. The amount of increase is not known but probably is no more than twice the requirement of the normal state. The requirement in states of disease which interfere either with absorption of thiamine from the intestinal tract or with its utilization and storage in the liver is not known. It probably varies tremendously from one person to another and from time to time in the same person, depending on the severity of the pathologic processes encountered.

CLINICAL CONSIDERATIONS

ETIOLOGY

Deficiency may be either primary or conditioned. Primary deficiency is induced by an inadequate intake of thiamine. Inadequate intake arises from intake of food which originally contained too little thiamine or from intake of food from which thiamine has been lost in processing or cooking. Two groups of patients obtain too little thiamine unless supervised in this regard: (1) patients who are on diets severely restricted in calories, and (2) patients who are on diets restricted in variety because of food idiosyncrasies (elimination diet, colitis diet, ulcer diet, and gallbladder diet). Therapeutic diets of restricted nature, unless adequately supplemented, are likely to be deficient diets. In cases of diabetes in which insulin therapy has been inadequate, thiamine deficiency may develop when vigorous insulin therapy is employed. In such cases restoration of adequate carbohydrate metabolism has suddenly increased the need for thiamine. Thiamine deficiency occurs in cases of chronic and acute alcoholism but the trophic disorders involved are caused only in part by the concomitant thiamine deficiency, arising as a rule from deficient intake of protective foods in general.

Conditioned thiamine deficiency may be associated with the following conditions: (1) chronic diarrhea and steatorrhea and chronic inflammatory lesions of the intestine in which there is interference with the absorption of ingested thiamine; (2) necrobiosis of liver cells and trophic disorders of the intestinal mucosa which interfere with phosphorylation and storage of thiamine; (3) chronic and severe diuresis as in uncontrolled diabetes mellitus and diabetes insipidus and in the resolving anasarca of cardiac disease; (4) thyrotoxicosis, fever, and neoplastic disease which increase the requirement for thiamine; and (5) degenerative diseases such as arteriosclerosis, which interfere with normal exchange of nutrients including oxygen. The appearance of unilateral degeneration of nerves and abnormal sensitivity of muscles in persons who have a defective circulation (lymphatic, venous, or arterial) may possibly be conditioned by local interference with thiamine metabolism. It has not been proved conclusively that tissues of the aged use thiamine less effectively than do tissues of the young.[9]

Symptoms and Physical Signs

Many signs and symptoms have been observed in thiamine deficiency but none of them can be considered pathognomonic, for other disorders associated with defective respiratory exchange may produce similar clinical features. The classic syndrome of beriberi could not be induced in man by acute and severe deprivation of thiamine, for the subjects quickly became prostrated and it became necessary to discontinue the experiments. Prolonged, moderate restriction of thiamine caused a general impairment of physical and mental health. The nearest approach to the clinical picture of beriberi was observed when thiamine was restricted to 0.1 mg. per 1000 calories, but a "partial periodic cure" was effected by injecting 1.0 mg. of thiamine subcutaneously at intervals of fifteen to twenty days. The partial periodic cure served to restore flagging appetites and to maintain a better level of physical activity. The following description and the data in Tables 28 and 29 are based on studies of induced deficiency of thiamine in man conducted by the authors or with which the authors were associated in some capacity.

GASTROINTESTINAL TRACT

Loss of appetite which may progress to nausea and vomiting at irregular intervals was a constant finding. Emesis would occur from one to three hours after a meal. On some occasions undigested food of the previous meal was vomited whereas at other times only gastric juice was vomited. Roentgenologic examination of the gastrointestinal tract revealed delayed emptying of the stomach and pooling of the barium sulfate meal in various segments of the small intestine, that is the so-called stepladder pattern (see XI*e* and *f*, p. 97). Constipation was the rule. It appeared to be significant that the height of nausea coincided with the peak level of the pyruvate observed in the blood after a meal of mixed foods or of glucose. This fact supported the opinion that the anorexia was caused by a chemical stimulus. In addition it was observed that intravenous injection of pyruvate caused nausea and vomiting. The intermittent character of the anorexia suggested that central chemical stimulation rather than neuropathy of the autonomic nervous system was responsible.

NERVOUS SYSTEM

Moderately severe and severe restriction of thiamine (0.2 to 0.1 mg. per 1000 calories) provoked many complaints. Anorexia, soreness, and weakness of muscles, clumsiness of the legs, paresthesias, bandlike feelings, and sensations of stinging and crawling were based possibly on disturbances of the physiology of peripheral tissues. However, early in the course of the deprivations there were unmistakable symptoms of disturbances of higher nervous centers, manifested in irritability, forgetfulness, difficulty in orderly thinking, disturbing dreams, vague fears, uneasiness, and development of ideas of persecution. De Wardener and Lennox[18] laid emphasis on the cerebral manifestations of thiamine deficiency among patients at the Singapore Prisoner-of-War Hospital and reported their observations in an article entitled "Cerebral beriberi." They noted anorexia, vomiting, nystagmus, emotional changes, gross

TABLE 28.* DEVELOPMENT OF BIOCHEMICAL DEFECT OF THIAMINE DEFICIENCY IN SUBJECT 1**

Day of period	*Excretion of thiamine in 24 hr.* (micrograms)	*Excretion of test dose of 1 mg. of thiamine hydrochloride in 4 hr.* (micrograms)	*Thirty minutes after administration of dextrose,* (mg. per 100 cc.)		*Patellar tendon reflex†*	*Achilles tendon reflex†*	*Ability to rise from squatting position†*	*Symptoms or signs which were persistent*
			Pyruvic acid	Lactic acid				
					Period of Preliminary Observation			
52	480	538	0.86	11.9	0	0	0	None
					Period of Restriction of Thiamine			
10	19	200	—	—	0	0	0	None
30	10	113	1.38	14.9	0	0	0	Anorexia, weakness
50	6	64	—	—	0	0	−1	Nausea, weakness, epigastric pain
70	11	101	1.84	18.7	0	0	−1	Nausea, weakness, sensation of numbness below knees
90	14	13	2.18	15.4	+2	−1	−2	Weakness, giddiness, occasional emesis, sensation of numbness below knees
110	10	20	—	—	−3	−4	−3	Frequent emesis, extreme weakness, apathy, frequent stumbling, sense of touch and vibration impaired below knees
120	8	39	3.19	15.6	−4	−4	−4	Loss of weight, mental confusion, prostration, sense of touch and vibration impaired at knees and ankles, paralysis of quadriceps femoris
					Period of Intensive Treatment with Thiamine Hydrochloride‡			
10	—	—	1.48	11.0	−4	−4	−4	Return of appetite, no further loss of weight, less mental confusion, paralysis of quadriceps femoris
30	—	—	1.35	13.0	−4	−4	−4	Good appetite, gain in weight, less mental confusion, return of interest, paralysis persistent

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* From WILLIAMS, R. D., MASON, H. L., POWER, M. H., and WILDER, R. M.: Induced thiamine (vitamin B_1) deficiency in man; relation of depletion of thiamine to development of biochemical defect and of polyneuropathy. *Arch. Int. Med.* 71:38, 1943; (Table 2, page 48).

** A woman aged 36, 168 cm. tall, weighing 56.5 Kg.

† 0, normal, and −4, absent.

‡ More than 60 mg. of thiamine hydrochloride per day.

Table 29.* RESULTS OF THIAMINE RESTRICTION
From July 25, 1940, to Jan. 13, 1941, in a Woman Aged 23, 172 cm. Tall**

	Diet								
	Grams				*Thiamine*	*Thiamine hydrochloride supplement*	*Thiamine excreted in urine*	*Body weight*	
Period of study	Carbohydrate	Protein	Fat	Calories	(micrograms)	(micrograms)	(micrograms)	(Kg.)	*Clinical status of subject*†
Preliminary	278	60	75	2027	856	——	90	64.0	Asymptomatic, well adjusted to regimen, congenial, industrious, efficient, vigorous; basal metabolic rate 0.0%; 4,900,000 erythrocytes
July 25, 1940 to September 23	335	62	57	2101	466	——	11	61.0	Works slowly; neglects work; follows instructions inaccurately; forgetful, irritable, quarrelsome; appetite capricious; basal metabolic rate −23%
September 24 to November 18	378	64	65	2353	475	——	24	61.4	Weeps and laughs alternately; self depreciatory; displays apathy, confusion, fatigue; works irregularly; complains of formication, pain in epigastrium, numbness of hands and feet; basal metabolic rate −16%; frequent emesis
November 19 to Jan. 13, 1941	403	62	82	2598	482	——	28	62.7	Unable to work because of dizziness and weakness; displays hopeless attitude; confused, bewildered, vacillating with apathy alternating with agitation, depressed; blood pressure 98/65; pallor and giddiness on standing; T waves of lead Cr-2 inverted; premature systoles; hands and feet cold and mottled; basal metabolic rate −14%
January 14 to February 27	405	63	85	2637	480	200 400	51 101	64.5	Continues to be depressed, restless, worried, definitely less apathetic; does not grasp instructions; displays lack of dexterity; appetite capricious with occasional emesis; insomnia; blood pressure 110/72; no pallor or giddiness on standing
February 28 to April 4	400	63	86	2626	484	600 800	190 202	64.8	Gradual improvement; assists with ward work; tires easily; cheerful at times, apathetic at others; sleeps fitfully; appetite consistently good; basal metabolic rate −24%
April 5 to May 2	366	62	85	2477	486	1000 1200	287 557	66.0	Congenial, cooperative, industrious; works more vigorously; no complaints, no physical defects; basal metabolic rate −24%
May 3 to May 30	360	63	66	2286	480	1400 1600	589 730	67.0	Asymptomatic, agreeable, efficient, vigorous; basal metabolic rate −19%; 4,270,000 erythrocytes

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* From Williams, R. D., Mason, H. L., Smith, B. F., and Wilder, R. M. Induced thiamine (vitamin B_1) deficiency and the thiamine requirement of man; further observations. *Arch. Int. Med.* 69:721, 1942; (Table 3, page 727).

** This is one of the subjects who were given large doses of thiamine hydrochloride prior to the study of thiamine requirements.

† The clinical notes apply to the condition of the subject at the end of the period to which they are appended.

mental changes, and ophthalmoplegia, correctable by early and vigorous treatment with thiamine.

Objective evidences of abnormality were manifested in the subjects of experimentally induced thiamine deficiency by various neuropathies. Areas of decreased perception of pinprick, light touch, and minor variations of temperature were found especially over the anterior surfaces of the legs and thighs. These areas corresponded to the surface distribution of nerves to the skin. Perception of vibrations of the tuning fork (128 vibrations per second) was impaired at the great toe, ankle, and knee. Lastly, severe weakness or paralysis of muscles of the legs appeared. The peroneal and the quadriceps femoris muscles were the principal muscles affected. Difficulty in squatting and rising was observed. The patellar and Achilles-tendon reflexes first increased and then, after a variable time, disappeared. Rarely, in the phase before paralysis occurred, stimulation of the plantar surface of the foot caused fanning of the toes and extension of the great toe. This response to plantar stimulation had a resemblance to the Babinski reflex which one finds in pyramidal tract disease. In the subject who demonstrated this phenomenon in greatest degree the concentration of pyruvic acid in the spinal fluid was 1.25 mg. per 100 cc. Proprioceptive responses were impaired because of weakness of the muscles of the legs, but a real defect of the sense of position of the extremity was not established. The large nerve trunks were irregularly sensitive, but most of this apparent sensitivity could be attributed to the sensitivity of adjacent tissues, especially muscle. Stimulation of the soles of the feet often elicited a delayed but very painful response. In our experience the sensory disturbance had the general features of "stocking and glove type" and corresponded to superficial skin innervation. However, on many occasions it corresponded more closely to the cutaneous dermatomes of Head and of Foerster. In those instances in which it extended as high as the middle of the thigh, the subject also had some disturbances of sensation in the hands. The upper extremities, however, were rarely affected and, unlike other neuropathies, the disturbances observed were bilateral.

MUSCULATURE

The calves and thighs were extremely sensitive to pressure. Soreness and aching of muscles of the calves and an intermittent claudication type of pain on climbing stairs were frequently encountered. The muscles of the legs were easily fatigued in standardized exercise tests. Muscles of the upper extremity and back (rowing) were almost as easily fatigued as were the muscles of the legs, but soreness and aching of muscles of the arms were rare complaints even in severe states of the deficiency.

CARDIOVASCULAR SYSTEM

The subjects usually complained of weakness, shortness of breath, consciousness of the heart beat, irregularities of the heart beat, marked discomfort in the thorax after exertion, and dizziness and giddiness on arising from the recumbent position. Common findings were low blood pressures (systolic values of 80 to 100 mm. of mercury and 40 to 60 mm. of mercury diastolic), sharp decrease of blood pressure, pallor, giddiness and swaying when the erect posture was assumed, and slow pulse rates at rest (50 to 60 per minute) but rapid pulse rates after exertion. The heart sounds were faint. Peripheral pulsations had a slapping quality. The skin of the hands and feet had a dusky red appearance. The circulation time was slightly decreased; in a few cases it was markedly decreased. The diameters of the heart and the venous pressures were normal. Electrocardiograms revealed premature ventricular systoles, marked sinus arrhythmia, prolonged A-V conduction time, and decrease in amplitude of ventricular complexes, the decrease being most marked in T waves of the apex leads (CF_2 and CF_4). Electrocardiographic changes were not found in every case and not continuously in the individual case. As a rule, they appeared during phases of sustained activity and disappeared during periods of rest in bed. Edema, not only of the extremities but also of the face, was observed in a number of instances; it was not constantly present and did not seem to depend on cardiac failure or on a decrease in the concentration of serum proteins. It may have been related to abnormal capillary permeability or abnormal retention of sodium and water. However, the electrolyte pattern of the plasma was not disturbed.

Dilatation of the heart, especially to the right side, valvular incompetence, and enlargement of the liver are observed in spontaneously occurring beriberi heart disease. Wintrobe's microscopic studies of the hearts of thiamine-deficient pigs revealed foci of necrosis in the auricular and ventricular musculature as well as in the cardiac septa. Focal or diffuse necrosis of myocardial fibrils was present, and leukocytic infiltration was found in some areas. The vagus nerves were normal. It is apparent from Wintrobe's observations that thiamine deficiency can cause defects of the myocardium and that these defects can cause myocardial failure. Undoubtedly, thiamine deficiency reduces the energy available from carbohydrate catabolism and in a somewhat nonspecific way reduces the capacity of the heart to perform work. If striated muscles were stimulated to contract repeatedly over long periods in thiamine deficiency, they might undergo a similar type of degeneration.

LABORATORY FINDINGS

There are few tests of an objective nature for detecting thiamine deficiency. Abnormalities of the electrocardiogram such as have been described are irregular in appearance and relatively nonspecific in character. Other conditions such as anoxia and toxemia induce similar patterns. Abnormality of gastrointestinal motility can be demonstrated in certain cases but is not specific for thiamine deficiency. The stepladder pattern is also observed in sprue and partial intestinal obstruction. Measurement of the metabolic defect of pyruvic acid and lactic acid metabolism following a "metabolic load" of glucose or of exercise, and measurement of urinary excretion of thiamine, are the principal laboratory procedures available.

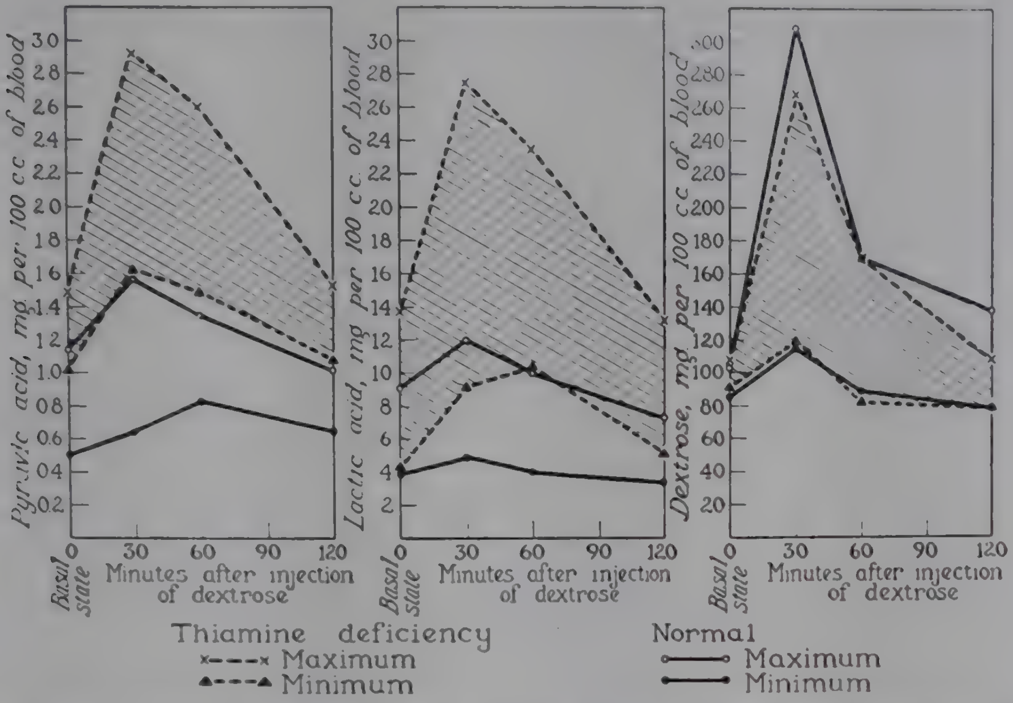

Fig. 25. The range of values for pyruvic acid, lactic acid and dextrose in the blood after intravenous administration of dextrose (0.4 Gm. of dextrose per kilogram of body weight in three minutes). Data for "normal" were obtained in studies on 12 physically normal subjects who were known to have been well supplied with thiamine and otherwise received the same nutrients as the thiamine-deficient subjects. Data for "thiamine deficiency" were obtained in studies on 7 subjects who had been maintained for periods of various duration on standard diets which provided either 0.1 or 0.2 mg. of thiamine per thousand calories and who, therefore, were known to be in states of thiamine deficiency. (From Williams, R. D., Mason, H. L., Power, M. H., and Wilder, R. M.: Induced thiamine [vitamin B_1] deficiency in man; relation of depletion of thiamine to development of biochemical defect and of polyneuropathy. *Arch. Int. Med.*, 71:38-53, 1943. [Fig. 1, p. 42.])

The following procedures performed with the subject in the basal state have been shown to be useful. Dextrose, 0.4 Gm. (0.8 cc. of 50 per cent solution of dextrose) per Kg. of body weight is injected intravenously in three minutes. Samples of blood for analysis of the content of pyruvic acid, lactic acid, and dextrose are obtained just before the injection and

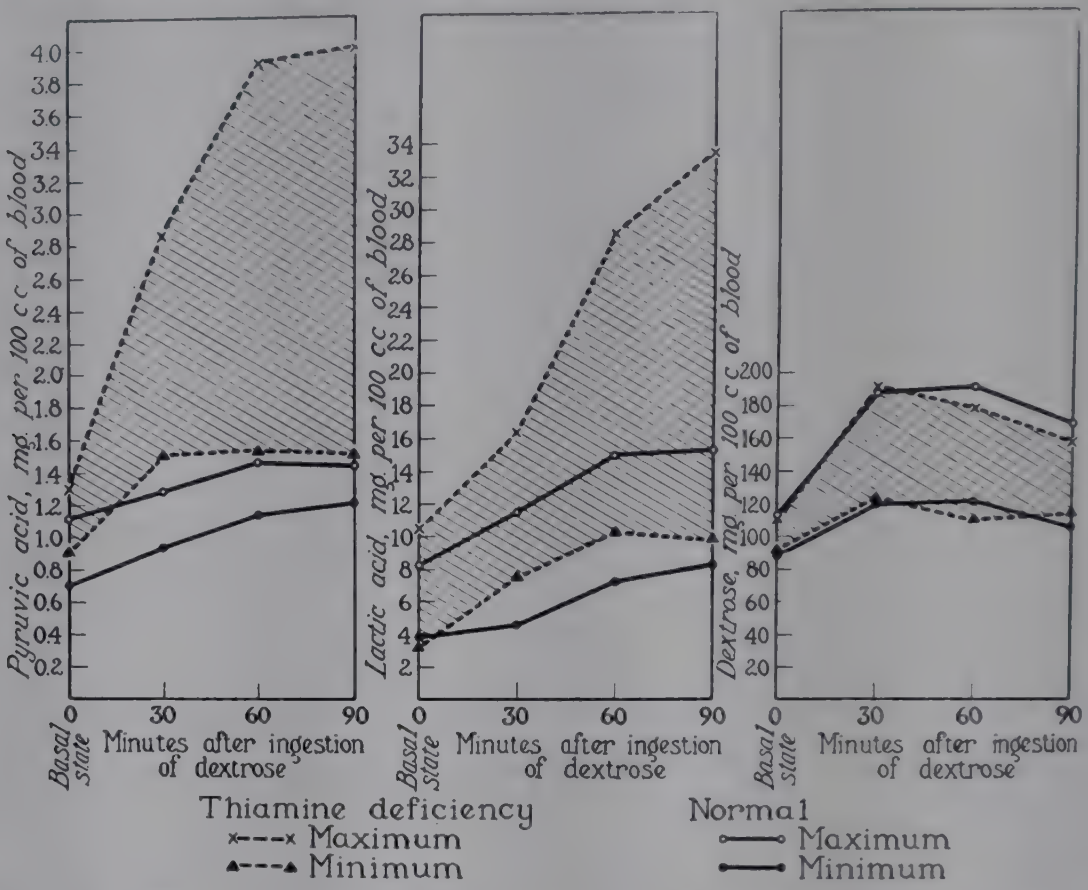

FIG. 26. The range of values for pyruvic acid, lactic acid and dextrose in the blood after oral administration of dextrose (50 Gm. dextrose in 250 cc. of solution at zero time and 50 Gm. at thirty minutes). Data for "normal" were obtained in studies on 11 physically normal subjects who were known to have been well supplied with thiamine and otherwise received the same nutrients as the thiamine-deficient subjects. Data for "thiamine deficiency" were obtained in studies on 10 subjects who had been maintained for periods of various duration on standard diets which provided either 0.1 or 0.2 mg. of thiamine per thousand calories. Thus, these subjects were known to be in states of thiamine deficiency. (From Williams, R. D., Mason, H. L., Power, M. H., and Wilder, R. M.: Induced thiamine [vitamin B_1] deficiency in man; relation of depletion of thiamine to development of biochemical defect and of polyneuropathy. *Arch. Int. Med.*, 71:38-53, 1943. [Fig. 2, p. 43.])

later at intervals of thirty, sixty, and one hundred and twenty minutes. The values for pyruvic and lactic acids at thirty minutes have the greatest significance. This intravenous test is used when nausea prevents oral administration of the dextrose. For the oral test, 50 Gm. of dextrose in 250 cc. of water is administered and thirty minutes later another 50 Gm. of dextrose is given, as in a dextrose tolerance test as performed by Exton and Rose. Samples of blood are obtained just before the first dose of dextrose and at thirty, sixty, ninety and one hundred and twenty minutes after its ingestion. The values for pyruvic and lactic acids and dextrose are most significant at sixty and ninety minutes. An earlier detection of thiamine deficiency is possible with the larger metabolic load of 100 Gm.

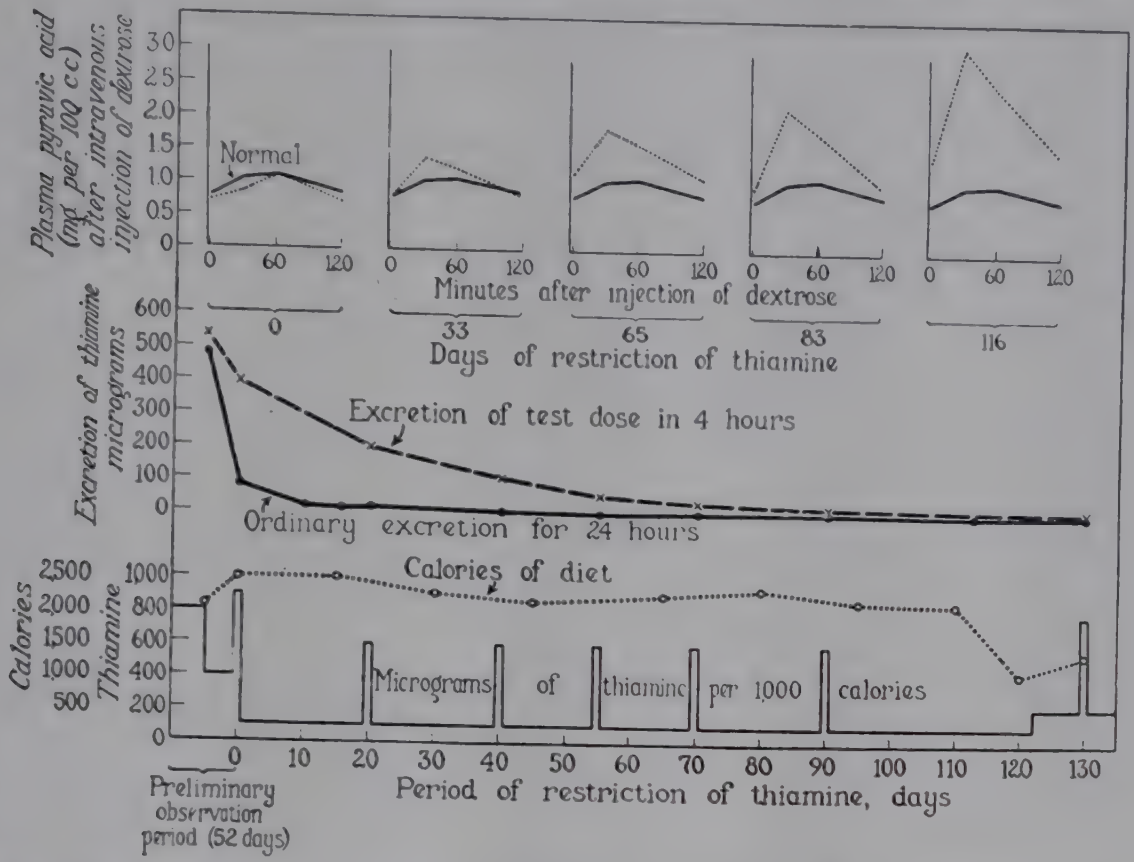

FIG. 27. Intake and excretion of thiamine; excretion of a test dose of thiamine (1.0 mg. thiamine hydrochloride was injected subcutaneously; the excretion in four hours after injection was determined; the subject was fasting), and data on pyruvic acid in the whole blood (not plasma as indicated in the figure) after intravenous administration of dextrose. (From Williams, R. D., Mason, H. L., Power, M. H., and Wilder, R. M.: Induced thiamine [vitamin B_1] deficiency in man; relation of depletion of thiamine to development of biochemical defect and of polyneuropathy. *Arch. Int. Med.*, 71:38-53, 1943. [Fig. 3, p. 46.])

of dextrose of the oral test. Division of the total dose of dextrose, as described, has reduced the incidence of emesis, a frequent complication of the test in severe thiamine deficiency. However, other investigators have used a somewhat larger amount of dextrose (1.75 Gm. per Kg. of body weight) given in a single dose with results substantially the same as ours. Horwitt and his colleagues[9] described a more elaborate metabolic load test which offers promise of broad clinical usefulness in the diagnosis of early or mild and cryptic states of thiamine deficiencies. This involves subjection of the subject to a mild exercise load sixty minutes after giving glucose orally. By considering the normal relationships of glucose, lactic acid, and pyruvic acid in the blood which obtain as a result of the combined glucose-exercise test they arrive at a formula and calculate an index of carbohydrate metabolism. Objective evidence of polyneuritis was observed in every subject when this index exceeded 15, and in such cases the index dropped precipitously within a few days after restorative treatment with yeast was instituted. Such metabolic load tests are not specific for thiamine deficiency. Administration of dextrose to subjects with "alimentary glycosuria" and to other subjects with thyrotoxicosis has also provoked abnormally high values of pyruvic acid. The general nature of the data obtained in thiamine deficiency is shown in Figures 25 and 26. In general, the more severe the deficiency the higher is the value for pyruvic acid.

Another indirect measure of thiamine deficiency is the quantity of thiamine excreted in the urine. We have followed two technics for this determination (Fig. 27). With the first method, the patient is given a measured diet containing not more than 1.0 mg. of thiamine per twenty-four hours and the urine is collected for this period. An excretion of 100 micrograms or more in twenty-four hours represents a normal excretion. With the second method, a test dose of 1.0 mg. of thiamine is injected subcutaneously and the urine is collected for the ensuing four hours. Excretion of 200 micrograms is considered normal, whereas excretion of less than 100 micrograms has been associated with some other evidence of thiamine deficiency and excretion of less than 50 micrograms with clear evidence.

Tests involving excretion of thiamine necessarily depend on adequate function of the kidneys and cannot be relied on if the renal function of the patient is impaired.

DIAGNOSIS

The diagnosis of thiamine deficiency depends on the following data:

1. The presence of a clinical syndrome compatible with thiamine deficiency, symptoms and signs referring especially to the neurologic system, the cardiovascular system, and the striated muscles. One should bear in mind that deficiencies of other nutrients, organic diseases of several categories, and states of toxemia from many causes can mimic the syndrome of thiamine deficiency.

2. A history of deficient intake of thiamine or detection of conditioning diseases which may predispose to thiamine deficiency.

3. Determination of excretion of thiamine while the patient is receiving a dietary intake of 1.0 mg. of thiamine per day, or determination of ex-

cretion of thiamine in a period of four hours following subcutaneous injection of a test dose of 1.0 mg. of thiamine.

4. Demonstration of abnormal values for pyruvic and lactic acids in the blood after giving a metabolic load test of dextrose, when conditions other than thiamine deficiency which may cause abnormal values for pyruvic and lactic acids have been ruled out.

5. A favorable response to adequate and prolonged therapy with thiamine. It must be emphasized that thiamine deficiency is rarely an isolated phenomenon and that other nutrients may be necessary for the adequate functioning of thiamine. It must also be emphasized that if anatomic derangement has occurred as a result of thiamine deficiency, even adequate therapy may never correct the defects.

TREATMENT

In most cases of acute thiamine deficiency there is a background of a chronic thiamine deprivation which has impaired the organism to such a degree that some anatomic derangement has occurred. The acute, biochemical defect is largely correctable in the course of a few days. However, when anatomic defects have appeared, as in the case of advanced neuropathy or cardiac failure, weeks or even months may be required to effect a cure. In many instances of severe thiamine deficiency the defects are irreversible. Neuropathy persists, mental and emotional changes persist, or the heart never regains compensation.

The treatment of thiamine deficiency implies two phases of therapy. In the first phase, which requires one to two weeks, emphasis should be given to "flooding" the organism with thiamine in doses of at least 10 mg. three or four times per day, preferably by the parenteral route. In the second phase, which requires several weeks to several months, emphasis should be given to a liberal allowance of thiamine (10 to 50 mg. per day) and to provision of other nutrients including other vitamins and protein, for it appears certain that once adequate thiamine metabolism is restored there is a relatively greater need for other metabolic factors.

It has been repeatedly demonstrated that even in cases of severe thiamine deficiency administration of as little as 5 mg. of thiamine per day is associated with excretion of large amounts of thiamine and that when the intake is large (50 to 100 mg. per day) a large percentage of the administered thiamine is excreted. From this it might be thought that use of such large amounts of thiamine in treatment as are recommended here is not justified. However, although thiamine administered in small doses undoubtedly reaches the muscles and viscera in sufficient concentration, it has not been proved that an adequate amount of thiamine reaches the less vascular areas or the areas bounded by meningeal barriers when it is administered in smaller doses. A high concentration of thiamine may favor diffusion into such areas and, until factors affecting diffusion of thiamine are more precisely known, it is a safer practice to administer this vitamin in large doses.

It must again be emphasized that very severe biochemical lesions of thiamine deficiency can be corrected quickly but that months of intensive therapy are required to induce a maximal regression of the lesions. It appears quite probable that previously damaged tissues are more susceptible than normal tissues to later restriction of thiamine. This hypothesis depends on observations of patients who previously had evidence of moderate to severe thiamine deprivation. Such persons when subjected to a restricted thiamine intake showed signs and symptoms of deficiency earlier and more severely than did others. This observation further emphasizes the necessity of adequate and prolonged dietotherapy for patients who have suffered episodes of thiamine deficiency.

BIBLIOGRAPHY

1. Barron, E. S. G. "Mechanisms of carbohydrate metabolism: An essay on comparative biochemistry," in Nord, F. F., and Werkman, C. H. *Advances in Enzymology; and Related Subjects of Biochemistry*. New York, Interscience, 1943, vol. 3, pp. 149-189.
2. Brandon, W. L. The Cause and Prevention of Beriberi. London, Rebman, 1907.
3. Eijkman, C. Eine Beri Beri-ähnliche Krankheit der Hühner. *Virchows Arch. f. path. Anat.* 148:523, 1897.
4. Elsom, K. O., Lewy, F. H., and Heublein, G. W. Clinical studies of experimental human vitamin B complex deficiency. *Am. J. M. Sc.* 200:757, 1940.
5. Follis, R. H., Jr., and Wintrobe, M. M. A comparison of the effects of pyridoxine and pantothenic acid deficiencies on the nervous tissues of swine. *J. Exper. Med.* 81:539, 1945.
6. Funk, C. On the chemical nature of the substance which cures polyneuritis in birds induced by a diet of polished rice. *J. Physiol.* 43:393, 1911.
7. Funk, C. The etiology of the deficiency disease: Beri-beri, polyneuritis in birds, epidemic dropsy, scurvy, experimental scurvy in animals, infantile scurvy, ship beri-beri, pellagra. *J. State Med.* 20:341, 1912.
8. Grijns, G. Researches on vitamins, 1900–1911. Gorinchem. J. Noorduyn. en Zoon N. V., 1935.
9. Horwitt, M. K., Liebert, E., Kreisler, O., and Wittman, Phyllis Investigations of human requirements for B-complex vitamins. *Bull. National Research Council*, No. 116, 1948.

10. Keys, A., Henschel, A., Taylor, H. L., Mickelsen, O., and Brozek, J. Experimental studies on man with a restricted intake of the B vitamins. *Am. J. Physiol.* 144:5, 1945.

11. Jansen, B. C. P., and Donath, W. F. Isolation of anti-beriberi vitamin. *Mededeel. v. d. dienst d. volksgezondh. in Nederl.-Indië.* 1:190, 1927.

12. Jolliffe, N., Goodhart, R., Gennis, J., and Cline, J. K. The experimental production of vitamin B_1 deficiency in normal subjects: The dependence of urinary excretion of thiamin on the dietary intake of vitamin B_1. *Am. J. M. Sc.* 198:198, 1939.

13. Keefer, C. S. The beriberi heart. *Arch. Int. Med.* 45:1, 1930.

14. Melnick, D. Vitamin B_1 (thiamine) requirement of man. *J. Nutrition* 24:139, 1942.

15. Platt, B. S., and Lu, G. D. Chemical and clinical findings in beri-beri with special reference to vitamin B_1 deficiency. *Quart. J. Med.* n.s. 5:355, 1936.

16. Stotz, E. "Pyruvate metabolism," in Nord, F. F., and Werkman, C. H. *Advances in Enzymology; and Related Subjects of Biochemistry.* New York, Interscience, 1945, vol. 5, pp. 129-164.

17. Takaki, K. Results of preventive measures taken against Kakka among Japanese marine prisoners. Quoted by Brandon, W. L.[2]

18. de Wardener, H. E., and Lennox, B. Cerebral beriberi (Wernicke's encephalopathy): Review of 52 cases in a Singapore Prisoner-of-War Hospital. *Lancet.* 1:11, 1947.

19. Weiss, Soma, Occidental beriberi with cardiovascular manifestations; its relation to thiamin deficiency. *J.A.M.A.* 115:832, 1940.

20. Williams, R. R., and Cline, J. K. Synthesis of vitamin B_1 *J. Am. Chem. Soc.* 58:1504, 1936.

21. Williams, R. D., Mason, H. L., Power, M. H., and Wilder, R. M. Induced thiamine (vitamin B_1) deficiency in man: Relation of depletion of thiamine to development of biochemical defect and of polyneuropathy. *Arch. Int. Med.* 71:38, 1943.

22. Williams, R. D., Mason, H. L., Smith, B. F., and Wilder, R. M. Induced thiamine (vitamin B_1) deficiency and the thiamine requirement of man: Further observations. *Arch. Int. Med.* 69:721, 1942.

23. Williams, R. D., Mason, H. L., and Wilder, R. M. The minimum daily requirement of thiamine of man. *J. Nutrition* 25:71, 1943.

24. Williams, R. D., Mason, H. L., Wilder, R. M., and Smith, B. F. Observations on induced thiamine (vitamin B_1) deficiency in man. *Arch. Int. Med.* 66:785, 1940.

25. Wintrobe, M. M., Stein, H. J., Miller, M. H., Follis, R. H., Jr., Najjar, V., and Humphreys, S. A study of thiamine deficiency in swine; together with a comparison of methods of assay. *Bull. Johns Hopkins Hosp.* 71:141, 1942.

Chapter 19

RIBOFLAVIN MALNUTRITION

Grace A. Goldsmith

RIBOFLAVIN, formerly designated vitamin B_2 or G, is a water-soluble yellow pigment with green fluorescence, which is widely distributed throughout the plant and animal kingdoms. Our knowledge of the chemical nature, physiologic function, and nutritional importance of riboflavin was acquired by research in diverse fields, and it was not until the nineteen-thirties that findings were correlated and the role of riboflavin in animal and human nutrition became apparent. Chemical research dates from 1879 when Blythe[8] demonstrated a yellow green-fluorescent pigment in whey, which he called lactochrome. In 1925, Bleyer and Kallman[7] obtained concentrates of this pigment and described certain of its properties. However, the chemical nature of this material remained obscure and no great importance was attached to it by these early workers.

Nutritional research began early in the twentieth century when it was shown that certain unidentified dietary factors were necessary for the growth of rats. McCollum and Kennedy,[37] in 1916, suggested the designation "water-soluble B" for one of these factors. Until 1920 there was uncertainty as to whether the water-soluble growth substance for rats was identical with the anti-beriberi vitamin, but in that year Emmett and Luros[19] showed that the two factors were not equally susceptible to destruction by heat and should therefore be considered different substances. Following this, the work of numerous investigators, among them Goldberger and his co-workers,[20] established that vitamin B was not a single entity.

In 1926 Goldberger and Lillie[20] produced in rats a deficiency syndrome which resembled human pellagra. This syndrome was believed to be due to lack of the pellagra-preventive (P-P) factor but has since been shown to be largely the result of riboflavin deficiency. This new vitamin was designated "vitamin G" by American biochemists and "vitamin B_2" by British and German workers. These terms, vitamin G and vitamin B_2, were later applied to the entire heat-stable fraction of the vitamin B complex. This confusion in terminology persisted for many years.

In 1931 Bourquin and Sherman[11] proposed a method for the determination of vitamin G in various materials, using the rat as the experimental animal. This method was used extensively in the study of foods and pharmaceuticals and the potency of substances tested was expressed as Bourquin-Sherman units. Hogan and his co-workers[26] did much to clarify the picture of vitamin G (B_2) deficiency in rats and to separate it from vitamin B_6 (pyridoxine) deficiency.

In 1932, Warburg and Christian[58] described an oxidation enzyme obtained from yeast, which was yellow in water solutions and exhibited a green fluorescence. This yellow enzyme is probably present in all living cells and, because of its easily reversible oxidation-reduction reactions, functions in cellular respiration. Warburg and Christian were able to split this enzyme into a protein and a pigment component, thus separating and identifying, for the first time, the prosthetic or chemically active group of an enzyme.

In 1933 reports from several laboratories indicated a relationship between water-soluble, yellow, green-fluorescent pigments found in plant and animal products and vitamin B_2 or G (riboflavin). Ellinger and Koschara[17] suggested that these pigments, which had been noted in milk, liver, kidney, urine, muscle, yeast, and plant materials, were related to the yellow enzyme of Warburg and Christian. Booher[9] obtained concentrates from whey which promoted the growth of rats on vitamin-G-deficient diets. Kuhn and co-workers[33] isolated a pigment from dried egg albumin and reported that the crystalline product was active in supplementing the Bourquin-Sherman diet. These workers observed a parallelism between vitamin B_2 activity and the intensity of yellow color and green fluorescence of materials tested. They suggested the chemical group name of flavins for these pigments and proposed differentiating them according to source as ovo-, lacto-, and hepato-flavin. It was later found that these flavins were identical and, since they contained the pentose sugar d-ribose, the term riboflavin was adopted.

The synthesis of riboflavin was accomplished in 1935, almost simultaneously, by Kuhn and co-workers[34] and by Karrer and associates.[31] György[24] showed that the biologic activity of the synthetic product was identical with that of the naturally occurring vitamin. Theorell in 1934–

35[54] found that the chemically active group of the yellow enzyme of Warburg and Christian was flavin phosphate.

Riboflavin has been shown to be an essential growth factor for many species of animals, including man, and for some types of bacteria. Human riboflavin deficiency was first described by Sebrell and Butler[50] in 1938. The condition was produced experimentally in adult women who were given a diet similar to that used by Goldberger and Tanner in 1925[21] in the production of pellagra. Lesions of the lips (cheilosis) and of the skin of the nasolabial folds developed which were cured by the administration of synthetic riboflavin. The lesions appeared to be similar to those described by Stannus[52] in 1912 in association with pellagra in Nyasaland, to findings obtained by Goldberger and Tanner in 1925,[21] and to some of the lesions described by Landor and Pallister[35] in 1935 in cases of "vitamin B_2 deficiency" in Malaya.

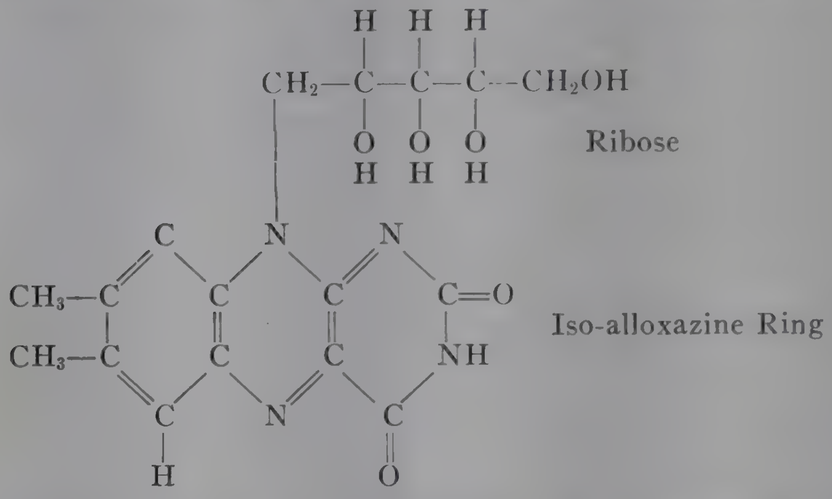

FIG. 28. Structural formula of d-Riboflavin (6, 7-Dimethyl-9-(d-l'-ribityl) iso-alloxazine).

Since 1938, human ariboflavinosis has been reported to occur frequently in various parts of the world.

CHEMISTRY AND PHYSIOLOGY

Riboflavin is a yellow, green-fluorescent pigment with the chemical formula 6, 7-dimethyl-9-(d-l'ribityl)-iso-alloxazine (see Fig. 28). The ribityl side chain relates riboflavin to the pentose sugars while its iso-alloxazine nucleus gives it certain chemical properties of a substituted benzine, an azine dye, and a pyrimidine.[10] Synthesis of derivatives of riboflavin have shown that only very limited alterations in molecular structure are compatible with retention of vitamin activity.

Riboflavin is water-soluble, quite stable in strong mineral acids and to oxidizing agents, but sensitive to alkali. It is irreversibly decomposed on irradition with ultraviolet rays or visible light.

Riboflavin is widely distributed in plant and animal tissues. Milk, liver, kidney, and heart are excellent sources, while many vegetables contain considerable amounts. Cereals are low in riboflavin but the content is increased markedly during germination. A dietary supply of riboflavin is apparently needed by all animals and by some types of bacteria and fungi, although others are able to synthesize it.

Riboflavin has a number of important functions in the human body and is presumably present in combined form in all human tissue cells. It has been shown to be a constituent of a number of enzyme systems associated with the intermediate metabolism of food, particularly of carbohydrates. The first enzyme which was found to contain riboflavin was the yellow enzyme of Warburg and Christian which assists in the oxidation of hexose-phosphoric acid. Riboflavin is also a constituent of amino acid oxidase, xanthine oxidase, and succinic acid dehydrogenase.[46] All of these enzymes function in oxidation-reduction reactions in the cells of the body.

The naturally occurring free form of riboflavin is readily absorbed from the small intestine. Excretion takes place through the urine and possibly to a minor extent through the intestinal tract. Even on high intakes only a small portion of ingested riboflavin is unabsorbed. The amount in the feces is relatively constant, presumably because of synthesis by bacterial flora.[47] Whether riboflavin so synthesized is absorbed and consequently supplements the dietary supply is largely unknown, although experiments by Najjar *et al.*[40] suggest such a possibility. In animal studies it has been shown that the character of the diet influences the degree of intestinal synthesis of riboflavin and other vitamins.[45]

The riboflavin content of tissues is reasonably constant, and saturation is readily attained under conditions of high intake. Reserves of riboflavin may be accumulated by the body, but they are not great and may be quickly lost. There are no special organs where riboflavin is stored but comparatively large amounts are found in human liver and kidney, 16 micrograms per Gm. and 20 to 25 micrograms per Gm. of tissue, respectively.[13] The quantity in muscle, which has been reported to be 2.0 to 3.0 micrograms per Gm.,[2] accounts for a large percentage of the total amount in the body.

The concentration of riboflavin in blood has been variously reported to be 0.35 to 0.50 micrograms per 100 cc. with little change in deficiency states.[2*] The urinary output varies greatly according to the intake.[14] In studies of normal persons values have ranged from 150 micrograms to

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[*] Recently, Burch, Bessey, and Lowry (*J. Biol. Chem.* 175:457, 1948) reported the following average values for riboflavin in the blood of well nourished adults: free riboflavin 0.8, total riboflavin 3.2 micrograms per cent in serum; total riboflavin 252 micrograms per cent in white blood cells and platelets, 22 micrograms per cent in red blood cells.

1 to 2 milligrams daily. It has been suggested that an output of about 200 micrograms in twenty-four hours is the lower limit of normal. When very large amounts of riboflavin are given, 50 to 85 per cent of the intake is excreted in twenty-four hours.[51] In studies of humans on restricted diets containing about 0.3 mg. of riboflavin per 1000 calories, or 0.7 to 1 mg. per day, the average excretion was between 12 and 14 per cent of the dietary intake.[32, 60]

REQUIREMENTS

A number of studies of the riboflavin requirement of both animals and man have been undertaken.[49] It has been estimated that an adult monkey can be maintained on an allowance of 15 to 20 micrograms per Kg. of body weight per day, and a rapidly growing monkey on twice this amount. A requirement of the same order of magnitude has been estimated for the dog: 25 micrograms per Kg. for the adult, and 40 micrograms for the growing animal. It is of course impossible to use these results directly in the estimation of human requirements because of such differences as size, surface area, metabolic rate, physical activity, type of intestinal flora, etc. Nevertheless, a general idea of requirement may be obtained in this way.

A number of metabolic balance studies have been conducted in humans on restricted diets in an endeavor to estimate human needs. In early experiments,[51] it was calculated from studies of urinary excretion that the requirement lay between 0.035 and 0.06 mg. per Kg. of body weight, or about 3 mg. daily. The Food and Nutrition Board of the National Research Council recommended a daily intake of 2.5 mg. for an active woman and 3 mg. for an active man, or roughly 0.9 mg. per 1000 calories. More recent studies have indicated that this figure was too high. Williams and co-workers[60] found no evidence of depletion of tissue stores in subjects receiving 0.8 mg. of riboflavin per 1000 calories (1.6 mg. per day), while a slight progressive decrease in urinary output occurred on diets containing 0.5 mg. per 1000 calories (1.0 mg. per day). They suggested a requirement between these two levels. No clinical evidence of deficiency occurred, however, with an intake of 0.35 mg. per 1000 calories, or 0.7 mg. per day, for 288 days. Keys *et al.*[32] found no signs of physiologic handicap in active men maintained for five months on diets containing 0.99 mg. per day (0.31 mg. per 1000 calories). However, as Parsons[49] has pointed out, there appeared to be a slow depletion of tissue stores in these men, as judged by urinary excretion, throughout the period of observation. From these and other data, Copping[14] concludes that available evidence suggests an allowance of 0.5 mg. per 1000 calories or 0.029 mg. per Kg. of body weight or 1.5 to 2.0 mg. per day for an adult. An additional supply is necessary for the actively growing child and during pregnancy and lactation. In 1945 the Food and Nutrition Board recommended an allowance of 0.6 to 0.7 mg. of riboflavin per 1000 calories for moderately active adult men or women, and an intake of 1.0 mg. per 1000 calories during pregnancy and lactation since satisfactory lactation has been shown to occur with this dietary supply.[48] Larger quantities are presumably needed during illness which puts a strain on metabolism but no exact data are available.

Recent evidence indicates that the riboflavin requirement is not intimately related to either caloric intake or physical activity. Accordingly in May, 1948, the Food and Nutrition Board proposed a single figure for the allowance of riboflavin in adults: 1.5 mg. for women and 1.8 mg. for men.

Long-term experiments with rats in Sherman's laboratory[18] have indicated that the total result of mild deficiencies of riboflavin may not be immediately apparent, and that the effects of a liberal intake in increasing nutritional well-being may be appreciated only in successive generations. Warkany[59] reported congenital malformations in rats when the maternal diet was deficient in riboflavin. These studies showed that a dietary intake which did not seriously depress growth or reproduction, interfered with the normal development of embryonic tissues. Such observations suggest that caution should be used in accepting findings in depletion experiments in adult humans as the sole basis for estimating nutritional requirements for optimal health. Allowances should be liberal until more information is available as a result of long periods of observation.

PATHOLOGY

A wide variety of manifestations of riboflavin deficiency have been reported in experimental animals in addition to failure of normal growth.[15, 18, 48, 59] In rats, findings consist of a dermatosis (dry, greasy scaliness of the skin with loss of hair), changes in the eyes including conjunctivitis, blepharitis, corneal vascularization and opacities, and the formation of cataracts, degeneration of nerve tissue, reduced hemoglobin formation, cessation of the estrus cycle and congenital malformations. Deficiency in swine is characterized by dermatitis, diarrhea, incoordination, nerve degeneration and cataract formation. In the young calf, lesions include hyperemia of the buccal mucosa, lesions of the corners of the mouth and along the edges of the lips, loss of appetite, scours, excessive salivation, and lacrimation. Symptoms in dogs consist of loss of weight, weakness, and ataxia, followed rapidly by inability to walk or stand, spastic extremities, coma, and death. This collapse syndrome is a late manifestation of deficiency. In young chicks prolonged partial riboflavin deficiency leads to "curled toe" paralysis, while complete deficiency induces an acute condition with paralysis and dystonia similar to the disease in dogs. The eggs of hens partially depleted in riboflavin do not hatch. Manifestations in the monkey[49] have been found to include asthenia, dermatitis, incoordination of the limbs, and a reduction in hemoglobin and white cells in the blood. Anemia has been reported in dogs as well as in monkeys, but in both species this symptom is probably due to deficiency of folic acid or some other factor. It has been demonstrated, however, that riboflavin is necessary for hemoglobin regeneration in dogs fed synthetic diets when the animals are subjected to long periods of bleeding.

A number of the findings in riboflavin deficiency in man are similar to those just enumerated for experimental animals. There may be conjunctivitis, changes in the cornea, dermatitis, and lesions of the lips and oral cavity. Up to the present time, nerve degeneration, cataract formation, and sudden collapse have not been reported.

Several other findings concerning riboflavin deficiency may be worthy of note.[48] Deficient mice succumb more rapidly to the intraperitoneal injection of virulent pneumococci than do normal animals. The incidence of a certain type of tumor produced by feeding "butter yellow" is increased when the intake of riboflavin is low. In riboflavin-deficient animals there is a reduction in the ability of the liver to inactivate estradiol. It has been suggested that a similar change, which may be of endocrinologic importance,[6] occurs in human deficiency.

A relationship between riboflavin and protein metabolism has been demonstrated in several species of animals.[41] When the protein intake of rats is low, the riboflavin concentration in the liver is reduced, and in riboflavin-deficient chicks, the protein content is less than in pair-fed controls. In humans, protein metabolism appears to affect riboflavin stores, as evidenced by a high excretion of riboflavin in 13 subjects during a four-day fast. Protein appears to be necessary for retention of riboflavin by the liver, and riboflavin utilization seems to be dependent not only on the intake of this vitamin but also on the amount of protein in the diet.

Very little is known of the manner in which riboflavin deficiency produces the pathologic changes observed in either man or animals. The sudden collapse which occurs in severe deficiency in animals is probably dependent on failure of important enzyme systems and hence failure of cellular respiration. Studies of enzyme activity in liver slices obtained from riboflavin-deficient animals showed a reduction in the ability to oxidize d-amino acids.[48] The addition of riboflavin dinucleotide (in vitro) restored this ability to normal. The activity of the enzymes xanthine oxidase and succinic dehydrogenase were also reduced in riboflavin deficiency. In animals where death occurred as a result of this deficiency state, the concentration of riboflavin in the liver, kidney, and heart was found to be one-third of that in normal controls.[13]

Histologic changes in the tissues have been studied in animals, but rarely in humans.[15] Anatomic changes in dogs have included fatty degeneration of the liver and, to a lesser degree, of the kidney, atrophy and deposits of fat in the bone marrow, nodular hemorrhagic areas in the lungs, and extensive, moderately severe degeneration of nerve cells in the brain and spinal cord, with myelin degeneration of fibers in the pyramidal tract and certain other structures. In chicks, degeneration of the sciatic nerve and patchy areas of degeneration in the spinal cord have been reported.

Lesions of the cornea in rats have been studied in detail by Bessey and Wolbach.[4] They described dullness of the cornea and a proliferation of vessels from the limbus which extended as an anastomosing plexus across the cornea, at first superficially and later in the deeper layers. The pathogenesis of corneal changes is not understood. It has been postulated that light destroys the riboflavin of the eye and that vascularization is a compensatory phenomenon. Another hypothesis places the primary defect in the lacrimal and meibomian glands, which are high in riboflavin, the cornea being affected secondarily through a diminution in the riboflavin content of the glandular secretions. Neither of these theories has been substantiated.[49]

Skin lesions in rats were described by Wolbach and Bessey[61] as a moderate keratosis, with atrophy of the sebaceous glands of the hair follicle and loss of hair due to separation of the basal portion of the shaft from the anchoring cells. Eddy and Dalldorf[15] found little more than atrophy of the skin, with a few round cells in the superficial corium. In tissue from a human subject with macerated, eroded lesions at the angles of the mouth, they noted an area of inflammatory reaction adjoining the sebaceous gland, with changes in the collagen and elastica causing a granular appearance.

The riboflavin content of muscle has been reported to be within the normal range in human deficiency.[2] The concentration in the blood has been found to be normal in one study, decreased in another. The urinary excretion is reduced both in twenty-four-hour periods and after test doses of riboflavin. These findings will be discussed in detail later in the section on laboratory diagnosis.

CLINICAL DEFICIENCY IN MAN

DEFINITION

Human ariboflavinosis is a nutritional disorder due to a deficiency of riboflavin and characterized by cheilosis, glossitis, lesions of the eye, and a seborrheic type of dermatitis.

ETIOLOGY

Ariboflavinosis is due to a dietary inadequacy of riboflavin or to some conditioning factor causing impaired absorption or utilization of this vitamin (see Chapter 1). This deficiency state may occur in any age group and is most often encountered in persons of poor economic status who consume a limited diet of high cereal content. Failure to eat foods which are rich in riboflavin, such as milk, meat, and fresh vegetables, either because of poverty, habit, or personal dislike, may lead to the development of this nutritional disorder. The intake of riboflavin must be low for many months before symptoms become evident. Signs of riboflavin deficiency often appear for the first time during periods of physiologic stress such as pregnancy and lactation,[12] or when growth is rapid during childhood.

Ariboflavinosis is frequently encountered in association with pellagra and, as a matter of fact, the signs of riboflavin deficiency were for many years considered to be part of the clinical picture of pellagra. Riboflavin deficiency is a common accompaniment of chronic debilitating diseases such as long-continued fevers, chronic congestive heart failure, and malignancy.[22] Any condition associated with an increase in metabolic rate, such as hyperthyroidism or fever, appears to increase the need for riboflavin and may precipitate symptoms, particularly if the previous diet has been inadequate. In debilitating diseases, poor appetite is almost universal and there may be interference with utilization of nutrients; storage may be poor and increased destruction may occur. Under conditions of pathologic stress as exemplified by severe acute surgical conditions, increased requirement and utilization of vitamins may occur.[36] Greig has demonstrated a breakdown in riboflavin coenzymes in shock.[43]

Gastrointestinal disorders are common precipitating or conditioning factors in the development of riboflavin deficiency. Nausea and vomiting interfere with food intake; diarrheal disorders such as amebic and bacillary dysentery, chronic ulcerative colitis, and regional ileitis, interfere with absorption from the intestinal tract. Short-circuiting operations on the gastrointestinal tract likewise lead to malabsorption. Deficiency may be precipitated postoperatively during the period of dietary restriction

Cirrhosis of the liver is often accompanied by signs of an inadequate supply of riboflavin, presumably due to improper utilization of this vitamin. Abnormalities in the absorption of riboflavin may occur in the absence of demonstrable organic disease of the stomach or intestines, as evidenced by therapeutic failure in certain patients unless the vitamin is given parenterally, and recurrence of symptoms when treatment is discontinued.

The exact incidence of ariboflavinosis is the subject of considerable controversy, but it appears to be a relatively common condition in many parts of the world. It is probably less frequent than was indicated by certain early reports, in which minor findings related to the eye and lips were considered to be definite evidence of this deficiency state. More rigid diagnostic criteria have been suggested by subsequent investigations. This should permit a more accurate record of incidence in future reports.

Signs and Symptoms

Early symptoms may be general in nature or related to the oral or ocular lesions. Soreness and burning of the lips, mouth, and tongue are common complaints, with exaggeration of the discomfort upon eating and swallowing. Highly seasoned foods may be particularly irritating. Visual symptoms include photophobia, lacrimation, burning and itching of the eyes, visual fatigue, and dimness of vision not related to errors of refraction. A sensation of grittiness similar to sand in the eyes is described by many patients.

Lesions of the lips begin with pallor and maceration at the angles of the mouth or with redness and denudation along the line of closure. The lips appear dry and chapped and, in severe deficiency, shallow ulcerations and crusting may occur. With progression of the angular lesions, transverse fissures appear which may extend outward from the buccal mucous membrane for a centimeter or more. The fissures are often covered with yellowish crusts which, when removed, leave a raw but nonbleeding surface. Linear scars may remain after healing occurs and the lips may become atrophic. The lesions of the lips and angles of the mouth have been designated cheilosis.[50] The characteristic fissures were described in the older literature under various terms such as perleche and marginal or angular stomatitis. At the present time a number of investigators prefer to use the designation "angular stomatitis" for the changes at the commissures. (See IX, p. 89.)

Cheilosis and angular stomatitis are not pathognomonic of riboflavin deficiency as they were once thought to be. In certain instances, therapy with riboflavin has been ineffectual, while the administration of niacin, pyridoxine, iron, ascorbic acid, or the whole vitamin B complex has resulted in resolution of lesions. Changes at the angles of the mouth may be due to poorly fitting dentures or to malocclusion of other causation.[16] Cheilosis on an allergic basis has also been reported.

The dermatitis of riboflavin deficiency begins most often in the nasolabial and nasamalar folds and spreads to the ala nasi and vestibule of the nose. It consists of a scaly, greasy dermatitis on an erythematous base. Considerable crusting may occur in late stages. Similar lesions may be found at the outer and inner canthi of the eyes and on the ears. Hard sebaceous plugs or fine filiform comedones may be seen over the bridge of the nose and on the malar prominences and chin. (See II, p. 61.)

An eczematous type of dermatitis of the scrotum and vulva has been described in association with riboflavin deficiency. Vaginitis has also been observed. Whether these lesions are due to lack of riboflavin or to other factors in the vitamin B complex is uncertain at present.

The tongue is characteristically purplish red or magenta in color (see VI*f*, p. 77), with a clean surface, and is often deeply fissured. The papillae may be swollen, flattened, and somewhat mushroom-shaped, giving a pebbled appearance to the tongue. In chronic deficiency of long duration, the papillae become atrophic. In these instances, it is impossible to differentiate the glossitis of riboflavin deficiency from that due to lack of niacin and as a matter of fact the two are usually associated.

The eye lesions of ariboflavinosis (see X, p. 93) have been the subject of extensive investigation and much controversy. Blepharitis, conjunctivitis, iritis, corneal vascularization, and opacities have been described.[53] The eyelids may be red, swollen, and matted together with a sticky exudate. The conjunctivae may be diffusely inflamed. Photophobia is often intense. Phlyctenular conjunctivitis has been described as occurring in association with riboflavin deficiency in China.[13] The corneal lesion consists of injection and proliferation of the vessels of the limbus, which may be seen at first only with a slit lamp, hand lens, or ophthalmoscope. Later, circumcorneal injection may be visible without magnification. Capillaries of the limbic plexus proliferate and extend into the superficial layers of the cornea, anastomosing to form tiers of loops. Superficial punctate opacities and superficial ulcerations of the cornea may occur. The latter can be demonstrated by staining the eye with fluorescein.[22] In later stages opacities may be found in the deeper layers of the substantia propria. Abnormal pigment deposits in the iris and even frank iritis have been described.

Early work led some to believe that corneal vascularization was specific evidence of riboflavin deficiency and, as mentioned previously, some reports of the prevalence of this nutritional disorder were based on slight changes observed in the blood vessels of the limbic plexus. Recent investigations have shown that many types of trauma and infection, as well as deficiency of several dietary factors (tryptophane, lysine, and vitamin A) can lead to invasion of the cornea by capillaries. Gregory[23] and Vail and Ascher[56] have discussed the normal anatomy and variations at the sclerocorneal junction, and the latter workers have pointed out that mild irritation can cause filling of previously invisible capillary loops. Numerous workers have failed to obtain a correlation between corneal vascularization and the dietary intake of riboflavin and have reported no improvement following the administration of this vitamin.[1] While there is good evidence that riboflavin deficiency can cause vascularization of the cornea, this finding cannot be taken as the sole criterion of ariboflavinosis. It has been suggested that corneal changes are likely to be of dietary origin only if the clear cornea is invaded by capillaries of the limbus; that in riboflavin deficiency changes occur in both eyes and involve the whole circumference of the cornea; and that circumcorneal injection may be absent until late stages when deep vascularization and opacities occur.[49] Whenever capillary invasion is due to lack of riboflavin, response to therapy, as evidenced by an emptying of the engorged capillaries, is noted within a few days.

There has been considerable discussion of the relationship between exposure to light and the requirement of ocular tissues for riboflavin. Studies of Tisdall, McCreary and their co-workers[55] suggest that such a relationship exists, but further study of this problem is needed.

Riboflavin has been administered as an adjunct in the therapy of corneal injury of various causation. Both positive and negative results have been reported. Riboflavin has also been used in the treatment of rosacea keratitis, again with variable results which on the whole have been disappointing.[42]

Machella and co-workers[38] have cited instances in which riboflavin therapy failed to relieve cheilosis, keratitis, dermatitis, and glossitis and have doubted the validity of the whole syndrome. However, data from many sources indicate that a deficiency of riboflavin can cause all of these findings although it is not the sole cause of any one of them.

Laboratory Findings

The urinary excretion of riboflavin may be determined by either fluorometric or microbiologic methods.[5, 39] In determining the status of riboflavin nutrition, the quantitative excretion has been measured in twenty-four hours, in one hour during fasting, and in several hours after the oral or parenteral administration of a test dose of riboflavin. While precise evaluation of the merits of these procedures is not possible at the present time, each may be useful in conjunction with clinical findings in arriving at a diagnosis of riboflavin deficiency. In normal persons the urinary excretion in twenty-four hours reflects, in general, the dietary intake of this vitamin and if the diet has remained relatively constant is indicative of tissue stores. The response to a test dose may be more informative as to tissue depletion or saturation. During starvation and rehabilitation, however, and under certain conditions of stress, the relationship of excretion to intake is complicated and somewhat remote. Hence, too much reliance should not be placed on excretion studies in evaluating riboflavin nutrition.

Normal persons have been found to excrete from about 150 micrograms to 2 mg. daily. An excretion of less than 200 micrograms in twenty-four hours has been considered to suggest an inadequate intake by some observers.[14] When diets are very low in riboflavin (0.5 mg. or less daily) the excretion usually falls below 100 micrograms. The excretion in one hour during fasting is considered a good index of nutritional status by several investigators.[28-30] Levels varying from zero to 20 micrograms in this period of time have been suggested as evidence of a deficiency state.

Considerable controversy exists concerning the value of load tests in assaying riboflavin nutrition. Both oral and intravenous tests have been devised. With a 5 mg. oral test dose, an excretion of less than 200 micrograms in four hours is considered by Johnson[29] to be evidence of tissue unsaturation or biochemical deficiency.

The concentration of riboflavin in the blood may be determined by either macro or micro procedures.[3] Axelrod and his co-workers[2] reported no difference between the concentration in normal and that in deficient subjects. Holt[27] found that riboflavin was absent in the serum and reduced in the cells of infants to whom diets free of riboflavin had been administered. Investigation of blood levels as a measure of riboflavin deficiency is deserving of further study.

DIAGNOSIS

The diagnosis of riboflavin deficiency is not always easy and should be made with caution unless several of the characteristic lesions are present at the same time. There are no pathognomonic signs of this nutritional disorder. Fissures at the corners of the mouth may be the result of malocclusion, while changes in the lips may be due to allergy or to the effects of wind and cold weather. In some instances, cheilosis may be induced by lack of dietary factors other than riboflavin. The glossitis may be confused with that of niacin, folic acid, or iron deficiency. Corneal vascularization of mild degree is found in well-nourished persons, while proliferation of the capillaries of the limbic plexus may occur as a result of trauma, infection, or an insufficient supply of several of the essential nutrients.

A careful dietary history may be of considerable assistance in the diagnosis of riboflavin deficiency. If the individual has been on a low intake of riboflavin for a long period of time, the diagnosis is more tenable. Careful search should be made for predisposing or conditioning factors, that is, for diseases which might increase the need for riboflavin or which might interfere with absorption or utilization of this vitamin. If laboratory facilities are available, determination of the urinary excretion of riboflavin is a useful diagnostic procedure.

At times, a critical therapeutic trial must be instituted. When the pure vitamin is administered, the subjective visual disturbances such as photophobia, burning, and lacrimation, disappear rapidly within twenty-four to seventy-two hours, as do soreness of the tongue and discomfort on swallowing. Within a few days, injection of the conjunctival and corneal blood vessels will subside and the lesions of the lips will begin to heal. Skin changes and glossitis respond more slowly, but marked improvement usually occurs within one to two weeks. In some patients there is a recurrence of symptoms and signs as soon as therapy is discontinued, even when an adequate diet has been instituted. The reason for this is not clear but may possibly be related to malabsorption.

The keratitis of riboflavin deficiency may be confused with syphilitic keratitis, but in the latter condition opacities and vascularization are often located posterially in the deeper layers of the cornea. Other evidence of syphilis, including positive serologic tests, may assist in the diagnosis. Infectious kerato-conjunctivitis must also be excluded.

The criteria which may be useful in arriving at a diagnosis of riboflavin deficiency may be summarized as follows: (1) An inadequate diet for a long period of time or the presence of some pathologic state which may be a predisposing or conditioning factor; (2) visual disturbances and soreness of the lips and tongue; (3) characteristic physical signs such as angular stomatitis or cheilosis, a magenta tongue, nasolabial seborrhea, and changes in the corneal and conjunctival blood vessels; (4) marked reduction in the urinary excretion of riboflavin; and (5) a prompt response to therapy with the pure vitamin. A combination of these findings, rather than any one abnormality, is essential if accurate diagnosis is to be made.

PREVENTION AND TREATMENT

The prevention of riboflavin deficiency is simple in principle, namely, the inclusion of a sufficient amount of this vitamin in the diet every day. This is difficult to attain in practice, however, particularly among the poorer groups of the population. In isolated areas where the types of food available are limited, or in persons whose dietary habits are poor through ignorance, custom, or prejudice, education is one solution of the problem. Children are more susceptible to nutrition teaching than are adults since food habits are not yet too deeply ingrained. The enrichment of certain staple foods, and the more equal distribution of protective foods in all parts of the world, are important preventive measures. Physicians can be of assistance by recognizing the presence of disease which may increase the need or interfere with the utilization of riboflavin and by recommending dietary changes which will meet these needs.

The treatment of riboflavin deficiency is similar to that of other nutritional disorders and includes the institution of an adequate diet and the administration of the vitamin in pure or concentrated form. The diet should include foods which are high in riboflavin and in other members of the vitamin B complex. (See Appendix Table C.) Such foods include milk, liver, lean meat, cheese, eggs, and green vegetables. Enrichment of flour and bread with riboflavin has contributed an important supply of this vitamin in diets of the low income group. Milk is the most important common source of riboflavin, a quart containing approximately 2 mg. A small amount of riboflavin is destroyed in the pasteurization of milk and on exposure to light during boiling (about 10 to 20 per cent).[44] There may be marked destruction by light after bottling, as when milk is allowed to stand on the doorstep. Riboflavin is fairly stable in ordinary cooking procedures. There is retention of 70 to 85 per cent in meat after roasting, braising, or boiling, and an additional 15 per cent has been recovered from the drippings. The concentration of riboflavin is maintained in dehydrated meat stored in vacuum tins for as long as ten months at temperatures up to 99°.[48] Some riboflavin is lost in the water in which vegetables are cooked.

The diet shown in Table 30 is high in protein and in all of the B vitamins and will furnish approximately 3 mg. of riboflavin and 2500 calories daily.

In cases of ariboflavinosis the vitamin should be administered orally in amounts of 5 mg. three times a day. This amount is usually sufficient to promote healing of the lesions and restoration of bodily stores to normal. In an occasional case, as much as 30 mg. daily may be necessary.

A few persons fail to respond to oral administration and in these instances riboflavin should be given parenterally. The usual effective dose is 5 mg. per day, preferably given intramuscularly. A large percentage is lost when the vitamin is administered intravenously. Riboflavin can be safely given by vein and should be so used, in conjunction with other vitamins of the B complex, in conditions where parenteral feeding must be carried out over long periods of time, such as postoperatively or in gastrointestinal disorders associated with vomiting and diarrhea.

TABLE 30. 2500-CALORIE DIET CONTAINING 3.3 MG. OF RIBOFLAVIN
FOODS TO BE EATEN EACH DAY

Foods	*Amount*	*Riboflavin content (mg.)*
Eggs	2	.34
Meat	2 large servings	.30
Milk	4 cups	.70
Cereal (enriched)	½ cup	.14
Bread (enriched)	6 slices	.90
Potato, white	½ cup or 1 medium	.04
Green leafy vegetable	2 servings (½ cup each)	.20
Yellow vegetable	1 serving (¾ cup)	.50
Citrus fruit or juice	1 cup	.20
Butter or margarine	3 tablespoons	—
	TOTAL	3.32

As indicated in the discussion of diagnosis, the manifestations of riboflavin deficiency respond rapidly to specific therapy in most instances, symptoms disappearing in a few days and lesions resolving in a matter of days to a few weeks. Some reports have indicated that prolonged therapy (one or two months) may be needed for disappearance of corneal vascularization.[55] The significance of this type of response has been questioned by other observers. In some persons it may be necessary to continue the administration of riboflavin if dietotherapy alone does not prevent recurrence of lesions.

Patients who have riboflavin deficiency often have signs of niacin and thiamine deficiency as well. In these instances the appropriate vitamins should be given in therapeutic doses. Some source of the entire vitamin B complex, such as dried brewers' yeast, wheat germ, or liver extract, may be a valuable addition to therapy. Yeast may be prescribed in doses of 1 or 2 tablespoons two or three times daily, to be taken in malted milk or tomato juice or otherwise disguised. Crude liver extract may be injected intramuscularly in amounts of 5 cc. one to three times weekly.

BIBLIOGRAPHY

1. Anderson, R. K., and Milam, D. F. Biomicroscopy of the eyes in evaluation of nutritional status. Corneal vascularization. *J. Nutrition* 30:17, 1945.
2. Axelrod, A. E., Spies, T. D., and Elvehjem, C. A. Riboflavin content of blood and muscle in normal and malnourished humans. *Proc. Soc. Exper. Biol. & Med.* 46:146, 1941.
3. Bessey, O. A., and Lowry, O. H. Biochemical methods in nutritional surveys. *Am. J. Pub. Health* 35:941, 1945.
4. Bessey, O. A., and Wolbach, S. B. Vascularization of the cornea of the rat in riboflavin deficiency, with a note on corneal vascularization in vitamin A deficiency. *J. Exper. Med.* 69:1, 1939.
5. Biological Symposia. Vol. XII. Lancaster, Pa., Cattell, 1947.
6. Biskind, M. S. Vitamins and Hormones, Vol. IV. New York, Acad. Press, 1946, p. 147.
7. Bleyer, B., and Kallmann, O. Beitrage zur Kenntniseiniger bisher wenig studierter Inhaltsstoffe der Milch (Kuhmilch), II. *Biochem. Ztschr.* 155:54, 1925.
8. Blythe, A. W. The composition of cow's milk in health and disease. *J. Chem. Soc. London* 35:530, 1879.
9. Booher, L. E. The concentration and probable chemical nature of vitamin G. *J. Biol. Chem.* 102:39, 1933.
10. Booher, L. E. The Vitamins. Chicago, A.M.A. 1939, Chapter XIII.
11. Bourquin, A., and Sherman, H. C. Quantitative determination of vitamin G (B_2). *J. Am. Chem. Soc.* 53:3501, 1931.
12. Braun, K., Bromberg, Y. M., and Brzezinski, A. Riboflavin deficiency in pregnancy. *J. Obst. & Gynaec. Brit. Emp.* 52:43, 1945.
13. Clements, F. W. Vitamins and Hormones, Vol. IV. New York, Acad. Press, 1946, p. 91.
14. Copping, A. M. Some aspects of riboflavin nutrition in man. *Nutrition Abstr. and Rev.* 14: 433, 1945.
15. Eddy, W. H., and Dalldorf, G. The Avitaminoses. (ed. 3) Baltimore, Williams and Wilkins, 1944, Chapter XVIII.
16. Ellenberg, M., and Pollack, H. Pseudoariboflavinosis. *J.A.M.A.* 119:790, 1942.
17. Ellinger, P., and Koschara, W. Ueber eine neue Gruppe tierischer Farbstoffe (Lyochrome). *Ber. d. deutsch. chem. Gesellsch.* 66:315, 1933.
18. Ellis, L. N., Zmachinsky, A., and Sherman, H. C. Experiments upon the significance of liberal levels of intake of riboflavin. *J. Nutrition* 25:153, 1943.
19. Emmett, A. D., and Luros, G. O. Water soluble vitamins. *J. Biol. Chem.* 43:265, 1920.
20. Goldberger, J., and Lillie, R. D. A note on an experimental pellagra-like condition in the albino rat. *Pub. Health Rep.* 41:1025, 1926.

21. Goldberger, J., and Tanner, W. F. A study of the pellagra-preventive action of dried beans, casein, dried milk and brewers' yeast with a consideration of the essential preventive factors involved. *Pub. Health Rep.* 40:54, 1925.
22. Goldsmith, G. A. Importance of vitamins of the B-complex in clinical medicine. *South. M. J.* 39:485, 1946.
23. Gregory, M. K. The ocular criteria of deficiency of riboflavin. *Brit. M. J.* 2:134, 1943.
24. Gyorgy, P. Ueber die Wachstumswerkung Synthetischer Flavinpraparate. *Ztschr. f. Vitaminforsch.* 4:223, 1935.
25. Handbook of Nutrition. Chicago, A.M.A. 1943.
26. Hogan, A. G. The Vitamins. Chicago, A.M.A., 1939, Chapter XIV.
27. Holt, L. E., Jr. Exhibit, New York Academy of Medicine Fortnight. October, 1947.
28. Holt, L. E., Jr., and Najjar, V. A. A simple method for the laboratory diagnosis of subclinical deficiencies of thiamine, riboflavin and nicotinic acid. *Bull. Johns Hopkins Hosp.* 70:329, 1942.
29. Johnson, R. E., Sargent, F., Robinson, P. F., and Consolazio, F. C. Assessment of nutritional and metabolic condition in the field. *War Med.* 7:227, 1945.
30. Kark, L. M., Aiton, H. F., Pease, E. D., Bean, W. B., Henderson, C. R., Johnson, R. E., and Richardson, L. M. Tropical deterioration and nutrition. Clinical and biochemical observations on troops. *Medicine* 26:1, 1947.
31. Karrer, P., Schopp, K., and Benz, F. Synthesen von Flavinen. IV. *Helvet. chim. acta.* 18:426, 1935.
32. Keys, A., Henschel, A. F., Mickelsen, O., Brozek, J. M., and Crawford, J. H. Physiological and biochemical functioning in normal young men on a diet restricted in riboflavin. *J. Nutrition* 27:165, 1944.
33. Kuhn, R., Gyorgy, P., and Wagner-Jauregg, T. Ueber Ovoflavin, den Farbstoff des Eiklars. *Ber. d. deutsch chem. Gesellsch.* 66:576, 1933.
34. Kuhn, R., Reinemund, K., Weygand, F., and Strobele, R. Ueber die synthese des lactoflavins (vitamin B_2). *Ber. d. deutsch. chem. Gesellsch.* 68:1785, 1935.
35. Landor, J. V., and Pallister, R. A. Avitaminosis B_2 *Trans. Roy. Soc. Trop. Med. & Hyg.* 29: 121, 1935.
36. Levenson, S. M., Green, R. W., Taylor, F. H. L., Robinson, P., Page, R. C., Johnson, R. E., and Lund, C. C. Ascorbic acid, riboflavin, thiamin and nicotinic acid in relation to severe injury, hemorrhage and infection in the human. *Ann. Surg.* 128:840, 1946.
37. McCollum, E. V., and Kennedy, C. The dietary factors operating in the production of polyneuritis. *J. Biol. Chem.* 24:491, 1916.
38. Machella, T. E., and McDonald, P. R. Studies of the B vitamins in the human subject. *Am. J. M. Sc.* 205:214, 1943.
39. Methods of Vitamin Assay. New York, Interscience, 1947.

40. Najjar, V. A., Johns, G. A., Medairy, G. C., Fleischmann, G., and Holt, L. E., Jr. The biosynthesis of riboflavin in man. *J.A.M.A.* 126:357, 1944.
41. Riboflavin metabolism. *Nutrition Rev.* 1:267, 1943; Protein metabolism and the vitamin B-complex. *Nutrition Rev.* 1:397, 1943.
42. The relation of riboflavin to ocular rosacea. *Nutrition Rev.* 2:110, 1944.
43. Vitamins in the therapy of shock and anoxia. *Nutrition Rev.* 3:89, 1945.
44. The destruction of riboflavin in milk by light. *Nutrition Rev.* 3:126, 1945.
45. Diet and riboflavin requirement. *Nutrition Rev.* 3:150, 1945.
46. Present knowledge of the vitamin B-complex in human nutrition. (Part I.) *Nutrition Rev.* 4:130, 1946.
47. Riboflavin and human nutrition. *Nutrition Rev.* 5:60, 1947.
48. Present knowledge of riboflavin in nutrition. *Nutrition Rev.* 5:227, 1947.
49. Parsons, H. T. Further studies on human requirements for riboflavin. *Federation Proc.* 3:162, 1944.
50. Sebrell, W. H., and Butler, R. E. Riboflavin deficiency in man. A preliminary note. *Pub. Health Rep.* 53:2282, 1938.
51. Sebrell, W. H., Butler, R. E., Wooley, J. G., and Isbell, H. Human riboflavin requirement estimated by urinary excretion of subjects on controlled intake. *Pub. Health Rep.* 56:510, 1941.
52. Stannus, H. S. Pellagra in Nyasaland. *Trans. Soc. Trop. Med. & Hyg.* 5:112, 1912.
53. Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M., and Kruse, H. D. The ocular manifestations of ariboflavinosis. A progress note. *J.A.M.A.* 114:2437, 1940.
54. Theorell, H. Reindarstellung (Kristallisation) des gelben Atmungsfermentes und die reversible Spaltung desselben. *Biochem. Ztschr.* 272:155, 1934. Reindarstellung der Wirkungsgruppe des gelben Ferments. *Biochem. Ztschr.* 275:344, 1935.
55. Tisdall, F. F., McCreary, J. F., and Pearce, H. Vascularization and symptoms of eye fatigue in R.C.A.F. personnel. *Canad. M. A. J.* 49:5. 1943.
56. Vail, D., and Ascher, K. W. Corneal vascularization problems. *Am. J. Ophth.* 26:1025, 1943.
57. The Vitamins. Chicago, A.M.A., 1939.
58. Warburg, O., and Christian, W. Ueber ein neues Oxydationsferment und sein Absorptionsspektrum. *Biochem. Ztschr.* 254:438, 1932.
59. Warkany, J., and Schraffenberger, E. Congenital malformations induced by maternal nutritional deficiency. *J. Nutrition* 27:477, 1944.
60. Williams, R. D., Mason, H. L., Cusick, P. L., and Wilder, R. M. Observations on induced riboflavin deficiency and the riboflavin requirement of man. *J. Nutrition* 25:361, 1943.
61. Wolbach, S. B., and Bessey, O. A. Tissue changes in vitamin deficiencies. *Physiol. Rev.* 22:233, 1942.
62. Youmans, J. B. Nutritional Deficiencies. Philadelphia, Lippincott, 1941.

Chapter 20

NIACINAMIDE MALNUTRITION AND PELLAGRA

Tom D. Spies

No more dramatic disease than pellagra has ever come to the attention of the medical profession. The term pellagra, derived from the Italian *pelle agra* meaning rough skin, was first used in medical literature in 1771 by the Italian physician, Frapoli, who found the word in common use among the peasant population of Lombardy. The authentic history of the disease, however, begins somewhat earlier in northern Spain. In the year 1735, Caspar Casal, physician to King Philip V, recorded his observations on *mal de la rosa,* a malady prevalent among the peasantry in the province of Asturias and later shown to be the same disease as pellagra. Twenty years after Casal recognized the disease in Spain, Antonio Pujati reported its presence in northern Italy. Owing to the subsequent recognition of numerous cases throughout northern and central Italy, a special hospital for the treatment of pellagrins was established at Legano in 1784 by warrant of Joseph II of Austria.

During the course of the nineteenth century, the disease was observed in many other countries, chiefly in France, Egypt, and Rumania; but here, as in Spain and Italy, it was already widespread at the time of its recognition.

The tracing of its history among the English-speaking peoples is most interesting. Eberle's two-volume book on *Practice*, probably the most popular work in the United States a hundred years ago, makes no mention of the disease. Bennet's book, written in Edinburgh in 1867 on the practice of medicine and the most popular book in the English language at the time, does not discuss it. No mention is made of pellagra in the history of medicine by Johannes Herman Bass in 1885. Surgeon General Billings' *National Medical Dictionary* in 1890 defines pellagra as "an endemic disease of Italy characterized by chronic erythematous inflammation of the skin with digestive derangement and neuroses." Austin Flint's *Practice* in 1894 had nothing to say on the subject. *The System of Medicine*, edited by Clifford Albutt and published in 1900, has five pages on pellagra, much of it devoted to the thesis that the disease undoubtedly was caused by a diet of "bad maize." In this *System* is first encountered the use of the term *pellagra sine pellagra*. The first cases of pellagra in the United States were reported in 1864 by Dr. Gray in Utica, New York, and Dr. Tyler in Somerville, Massachusetts.

Men whose names will ever be connected with the discovery and accurate description of the disease in this country are Dr. George Searcy and Dr. E. L. McCafferty, physicians on the staff of the Institution for Insane Negroes at Mount Vernon, Alabama. In 1907 the country was startled by their brief report of an epidemic of pellagra in this institution. Their description of the disease was so accurate that within a few weeks after their report was published, pellagra was recognized in six states and its identity with Italian pellagra was irrevocably established.

A decade or so later Goldberger, Wheeler, and their associates[8] induced pellagra in 5 of 11 subjects by means of an unbalanced diet. Later they demonstrated that dried brewers' yeast, lean meat, and milk had pellagra-preventive value.[5] They also treated some cases of naturally occurring deficiency diseases with dried brewers' yeast.[6] Despite the application of this therapy, Boggs and Padget[1] and Spies[18] in the early 1930's reported a high mortality rate among severely ill pellagrins.

In 1935 Spies[16] reported that he had been able to reduce the mortality rate in severe pellagra from 54 to 6 per cent either by giving much larger doses of dried brewers' yeast than had been given previously or by administering parenteral liver extract and by being certain in every case that the patient ate a diet high in calories, protein, minerals, and vitamins. He concluded that Goldberger's recommended therapy of one ounce of dried brewers' yeast daily might be sufficient in the mild case but in the severe case much larger amounts of substances containing the pellagra-preventive factor were necessary.

CHEMISTRY AND PHYSIOLOGY

Soon after this, great interest began to center around the isolation and synthesis of some of the vitamins. The students of pellagra were soon to become interested in nicotinic acid.

This substance, the beta-carboxylic acid of pyridine, is an organic compound which was first prepared from nicotine in 1867 by Huber.[12] Many years later it was isolated from rice polishings by Suzuki, Shimamura, and Odake,[19] Funk,[4] and Williams.[26, 27] Vickery and others[20] found nicotinic acid in yeast. Warburg and Christian[21] and Kuhn and Vetter[13] isolated the amide of nicotinic acid from the red blood cells of the horse and from mammalian heart muscle, respectively. Spies and his associates[15] demonstrated conclusively that parenteral liver extract is an important therapeutic agent in human pellagra, and Goldberger and Sebrell established its curative value in treating canine blacktongue. Elvehjem, Madden, Strong, and Woolley[2] showed that nicotinic acid was curative in canine blacktongue and isolated it from liver extract. Independently and almost simultaneously, excellent results in treating human pellagra were reported by Spies, Cooper, and Blankenhorn,[17] Fouts, Lepkovsky, Helmer, and Jukes,[3] Smith, Ruffin, and Smith[14] and Harris.[11]

The growth rate of rats maintained on a diet low in protein is depressed by the replacement of part of the casein in the diet by corn products. When the diet contains sufficient niacin or tryptophane, then the corn products do not affect the growth unfavorably. Niacin and tryptophane participate in this effect interchangeably.

The metabolism of tryptophane in animal tissues is altered when the animal has pyridoxine deficiency. It is not fully settled whether tryptophane stimulates niacin synthesis in the rat or whether it is a precursor of niacin. Some studies suggest that there is a definite relationship between the maintenance of normal pyridoxine metabolism and the maintenance of the synthesis of niacin by the rat from tryptophane.

DIAGNOSIS

Pellagra, a specific metabolic disorder protean in its manifestations, worldwide in its distribution, and seasonal in its occurrence, is characterized clinically by a red, sore tongue, alimentary tract disturbances, and changes in the central and peripheral nervous systems and other systems. In fact, no tissues of the body are entirely exempt if the disease is permitted to run its natural course untreated.

Outside the endemic areas of pellagra, such as Italy, Spain, Rumania and the southern part of the United States, the diagnosis is seldom considered unless the classical "four D's"—dermatitis, diarrhea, dementia, and death—have occurred. Such classical cases are relatively uncommon and represent the end stage of a disease which should have been recognized weeks or months or years earlier and which is readily amenable to rational therapy.

Chief among the reasons for failure of diagnosis in most instances is the fact that most physicians, particularly outside the endemic areas, fail to think of pellagra. This is usually because the general features of this disease are relatively unknown. For example, few physicians realize that pellagra may occur in the debutante as well as in the indigent farmer and alcoholic.

Until a specific laboratory test for pellagra has been discovered, diagnosis must depend upon a reliable medical and dietary history and a careful physical examination. The physician should keep in mind that pellagra is particularly prevalent in the following three groups:

1. The indigent and those with erroneous dietary habits and dietary idiosyncrasies. Persons in this group who develop pellagra usually are designated endemic pellagrins. As a rule, an analysis of the dietary habits of these persons reveals that they have subsisted habitually and over a long period of time on a diet which is high in carbohydrate and fat and relatively low in protein, minerals, and vitamins. Usually the total caloric intake is low, and the patients have lost considerable weight. Occasionally, however, the caloric intake from foods high in carbohydrate and fat is high and the patient is overweight. Conspicuously lacking in the diets of these persons are lean meat, fish, eggs, milk, and fresh fruits and vegetables.

2. Persons who have organic diseases. The incidence of pellagra is especially high among persons with tuberculosis, diseases of the gastrointestinal tract, cirrhosis of the liver, heart disease, nephritis, diabetes, amebic dysentery, pneumonia, hookworm, influenza, typhoid fever, malaria, and other diseases interfering with the ingestion, assimilation, or utilization of the essential pellagra-preventive substances present in food. To persons in this group sufficient amounts of a well-balanced diet may have been available but because of their disease they either have lost their appetite or are unable to utilize the essential food substances. Even though they are undernourished from these diseases, however, the majority of these persons never have pellagra.

3. Persons with chronic alcoholic addiction. Pellagra is likely to develop in persons who consume large quantities of strong alcoholic beverages and fail to eat an adequate diet regularly. If the chronic alcoholic addict continues to eat an adequate, well-balanced diet regularly, he usually will not develop pellagra. In fact, the author has observed that pellagrins "can be cured even when given large amounts of whiskey if an adequate diet is ingested."

The symptoms, lesions, and methods of treatment are essentially the same irrespective of whether the disease has developed following poverty, erroneous dietary habits, dietary idiosyncrasies, organic diseases, chronic alcoholic addiction, or some combination of these various conditions.

A diagnosis of pellagra often is made easier if the following facts are in mind:

1. *General:* Pellagra is a noncontagious, nonhereditary, clinical syndrome occurring at any age in either sex of any race. It may appear in any stratum of society but is more common in the poorer classes. The incidence of the disease is much greater during the spring than at any other season of the year. Unless therapy is given rigidly and consistently, the disease characteristically recurs. Symptoms arise in the skin, the gastrointestinal tract, and the nervous system. These three systems are not necessarily all involved nor are they affected in any regular order. Pellagrins vary so greatly that identical cases rarely will be seen. Extreme variability likewise is shown in the order of appearance and in the severity of the individual symptoms present.

2. *Prodromal symptoms:* Prominent among the prodromal symptoms causing the patient to seek medical aid are insomnia; loss of appetite, weight and strength; soreness of the tongue and mouth; indigestion; diarrhea; abdominal pain; burning sensations in various parts of the body; vertigo; headache; numbness; nervousness; distractibility; flights of ideas; apprehension; mental confusion and forgetfulness. A search for diagnostic signs in such persons often leads to the recognition of pellagra at an early stage. Most patients with these early symptoms have no diagnostic signs of pellagra when they first are seen by the physician. He should suspect pellagra in such persons, however, and should make frequent observations for the appearance of diagnostic signs of the disease. In certain cases a clear-cut history of an inadequate diet may justify a tentative diagnosis of pellagra even in the absence of characteristic dermal or oral changes.

3. *The skin:* Typical dermal lesions are diagnostic of pellagra (see III *a, b, c, d, e,* and *f,* p. 65). They may appear any place in the body but are found most frequently over sites of irritation, such as the dorsum of the hands, wrists, elbows, face, neck, under the breasts, knees, feet, and in the perineal region. In almost every instance the lesions are bilaterally symmetrical and are separated from the healthy skin by a sharp line of demarcation. The dermal lesions are never static and vary greatly from one patient to another. In the early stages, examination usually reveals an erythematous area which closely resembles sunburn and often is accompanied by severe burning and itching. As the disease progresses, the area becomes swollen, tense, and redder. In some cases vesicles and bullae form and frequently rupture. After a period of time, varying from a few days to several months or years, desquamation

begins in the center of the lesion. By this time the erythematous lesion has become reddish brown and scaly. The lesion may desquamate either in large flakes or in fine, brownish white scales. Pigmentation, especially at the margins of the lesion and around the hair follicles, is prominent in many cases.

It must be realized that, although most pellagrins develop dermal lesions at some time during the course of their disease, there are some in whom lesions never appear. This form of the disease is known as *pellagra sine pellagra* (pellagra without the rough skin). The absence of these lesions should never deter the physician from initiating antipellagric therapy.

4. *The alimentary tract:* Characteristic glossitis and stomatitis are diagnostic of pellagra (see VI *b*, *c*, and *d*, p. 77). Usually they appear early in the course of the disease and are characterized by redness. In the early stages of pellagrous glossitis, the tip and lateral margins of the tongue are reddened and swollen. As the disease progresses, the swelling increases and the reddening becomes more intense. Deeply penetrating ulcers may appear along the sides and tip but they rarely are seen on the surface, this area frequently being covered with a thick, gray membrane filled with debris and Vincent's organisms. The tongue usually is hypoesthetic but it may be hypersensitive. The buccal membranes, the mucocutaneous surface of the lips, the gums, and the palate may be affected likewise and thus aid in the diagnosis of the disease. The course of these oral lesions is similar to that of the glossitis. A burning sensation of the tongue and of the mucous membranes of the pharynx, esophagus, and stomach which is sometimes aggravated by hot or acid foods often is present. Nausea, vomiting, and ptyalism may appear early in the course of the disease but one cannot rely on their presence in making an early diagnosis since, in the majority of cases, they are advanced symptoms.

About 60 per cent of pellagrins have achylia gastrica. In the majority of cases the bowels act regularly or are constipated, contrary to what is generally believed. Severe, persistent diarrhea tends to appear only in the more advanced cases. The stools may be hard, soft, or watery, but the odor is always foul. Persons with pellagra frequently complain of abdominal pain, discomfort, and distention, particularly after meals, symptoms which may be present at any stage of the disease.

5. *The nervous system:* The diagnosis of pellagra usually is made because of the presence of characteristic dermal or oral lesions but the presence of other symptoms, particularly those related to the nervous system, often aids in the diagnosis. In the early stages of the disease periods of depression and apprehension frequently occur, and the patient

may complain of increased irritability, insomnia, headaches, dizziness, muscular weakness, and bilateral burning of the extremities or other parts of the body. In the later stages of the disease, tremor, jerky movements, and rigidity of the body frequently accompany these mental symptoms. Alteration of the tendon reflexes is sometimes present; at first they usually are increased, later decreased and finally, in the later stages of the disease, they may be absent altogether. Numbness, and later paralysis of the extremities, particularly the legs, is a common finding. The more advanced cases of pellagra often are characterized by tremor and a spastic or ataxic gait which frequently is associated with peripheral neuritis. If the patient is not treated, insanity is likely to develop.*

PREVENTION

The prevention of pellagra is dependent chiefly upon the ingestion, assimilation, and utilization of adequate amounts of a well-balanced diet. The dietary method of prophylaxis is an outgrowth of years of earnest striving on the part of many investigators who sought to evolve successful methods for the treatment and prevention of the disease. As long ago as 1735, Casal, the first known writer on the subject, mentioned the poor diets consumed by the peasantry in the districts of Andalusia in northern Spain where pellagra was endemic. In 1866, Roussel, the most outstanding pellagrologist in France, stated that dietetic measures were of greatest importance in combating pellagra. During the latter half of the nineteenth and the first decade of the twentieth century when pellagra was so rife in Italy, the Italian government undertook extensive measures for the prevention of the disease. Since spoiled corn was accepted as being the cause of pellagra by most investigators at that time, these measures dealt mainly with the elimination of corn as the chief foodstuff in the diet. In 1902, the Italian government passed a law whereby all corn had to be inspected and tested and the sale of spoiled corn was prohibited. Desiccating plants and cooperative kitchens were established, agricultural methods were improved, and widespread public health education on the dangers of eating spoiled corn were undertaken. Magazines and pamphlets were distributed widely by the government, popular lectures were given, and colored lithographs which depicted the harmful results of eating spoiled corn were hung in public halls. Whether these measures were responsible for the decrease in the incidence of pellagra which occurred shortly thereafter has been a matter of some dispute. Niles pointed out that the peasants were faring better than they had at any previous time, their wages were higher, and they could afford a more varied diet. Furthermore, some of the peasants were emigrating temporarily and upon returning home were no longer contented with a monotonous diet of corn and its products. Lombroso (1869–97), the most ardent supporter of the spoiled-corn theory of etiology, advocated the elimination of corn from the diet and the addition of meat and milk.

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* For the association of pellagra and macrocytic anemia, see Chapter 21, p. 549.

Goldberger, Waring, and Tanner of the United States Public Health Service were among the first to demonstrate that pellagra can be prevented by means of proper diet.[7] These investigators also showed that it was some specific factor or factors, which they called the p-p (pellagra-preventive) factor, which protected against the development of the disease. Subsequent investigations revealed that many foodstuffs contained the pellagra-preventive factor.[5, 9, 10, 22-25] On the basis of these investigations, Goldberger and his associates recommended as a preventive measure a diet containing liberal amounts of these foodstuffs. In the years which have followed, these recommendations of Goldberger have been employed with increasing success, and other foods rich in the pellagra-preventive factor have been discovered.

Before entering upon a discussion of the manner in which pellagra may be prevented, it is well to realize that all cases of pellagra tend to fall into one or the other of the following two groups:

1. Endemic cases which arise from conditions more or less common to whole groups of people, such as members of households and institutional inmates. The conditions giving rise to the development of such cases include poverty, ignorance, a general lack of thrift, limitation of the kind and amount of food crops raised resulting in a restriction in the variety of foods available for home consumption, and subsistence on a one-sided and monotonous diet.

2. Sporadic cases which arise from conditions peculiar to the individual. This group includes persons who, because of dietary idiosyncrasies, food fads, chronic alcoholism, erroneous dietary habits, increased requirements, and the presence of other diseases, fail to ingest, absorb, or utilize adequate amounts of foods rich in the pellagra-preventive substance. Such cases may occur despite the fact that the patient's financial status is good and that an adequate diet is available.

Although we know that pellagra is associated with, and develops from, the continued ingestion of an improper diet, the problem of carrying out the measures necessary to reduce its incidence is a serious and a difficult one. In the first place, the persons among whom pellagra is most likely to develop are ignorant of what constitutes a proper diet. Secondly, they often are too poor to buy the foods which will protect them against the disease. For most of them it is a hand-to-mouth existence, especially in the rural districts. Wheeler and Sebrell[25] noted that of the 7146 deaths reported (based on the 1930 census), 7000 or 97.7 per cent occurred in states of the U.S.A. which lie wholly within the cotton-belt region. All of the available land is used for cotton, the main money crop, leaving little or none for growing vegetables for home use. Finally, the financial returns on the money crop are so low that these people can afford to buy little more than corn meal, molasses, salt pork, dried beans, and syrup through the country store or commissary.

The physician's problem then is twofold. He not only must devise means for widespread public health education whereby people will know what they should eat but also he must offer them practical means for obtaining it. Much can be done in directing people toward a knowledge of nutritional needs by physicians and workers in the public health service. Illustrated material on what constitutes an adequate diet should be distributed among these people, public lectures should be given in small communities, and radio programs should be instituted. Whenever possible, these people should be advised to change their diet to one containing large amounts of milk, lean meat, eggs, fresh vegetables and fruits, fish, and poultry. If they cannot afford this, they should be advised to decrease the amount of fats and carbohydrates in their diet and take large amounts of at least one of the pellagra-preventive foods. Four ounces of lean meat daily will prevent the disease. As substitutes for the meat or as additions to it, canned salmon, canned corn beef, liver, chicken, or smoked lean pork may be used. Potential pellagrins should be encouraged to keep a cow, hogs, and chickens and to devote a portion of their land to growing tomatoes, spinach, peas, kale, mustard greens, collards, and turnip greens. Instructions should be given in the method of avoiding loss of water-soluble vitamins through the processing and cooking of foods. Finally, wise spending of money for foods should be emphasized. The public health worker and the physician should offer practical dietary suggestions to members of a pellagrin's family and to any other potential pellagrins whom they contact.

If, for any reason, none of the above suggestions can be carried out, specific supplements must be furnished potential pellagrins by relief agencies. Those which are least expensive yet very effective are: 113 Gm. of wheat germ daily, 57 Gm. of yeast daily, or 50 mg. or perhaps much less of nicotinic acid amide daily. Nicotinic acid amide is the most powerful weapon we now have for combating the disease, and its use is advocated when a well-balanced diet is not available.

The prevention of sporadic cases which arise from conditions peculiar to the individual is essentially the same as that of endemic pellagra. Persons with any disease which affects the nutritional state of the body should be watched carefully by the physician. Those who are unable to ingest, absorb, or utilize normal amounts of essential food substances should be given specific therapeutic agents. These may be administered either orally or parenterally but the latter is recommended for patients whose absorption is greatly impaired. Wheat germ (113 Gm. daily), yeast (57 Gm. daily), liver extract (57 Gm. daily), and nicotinic acid amide (50 mg. daily) are very effective for oral administration. Although nicotinic acid amide is the most potent agent in protecting the patient from the development of pellagra, yeast, wheat germ, and liver extract are often to be preferred since they contain other essential dietary factors in addition to those which prevent pellagra. Obviously, proper treatment of the existing disease will greatly decrease the possibility of the patient's developing pellagra; hence, such treatment should be instituted immediately. The food intake of persons whose diets are restricted because of diabetes, obesity, epilepsy, heart disease, and other diseases requiring a modification of the normal diet, should be checked carefully to make certain that they are getting adequate amounts of all of the essential nutrients and, if they are not, supplements should be given. Whenever a person's requirement for nutrients is above the average because of pregnancy, lactation, hyperthyroidism, or increased physical exercise, supplements must be administered to meet the increasing needs. It is well to realize that many people live on the borderline of pellagra and decrease in the intake of the anti-pellagra substance in the diet, however slight, if maintained over a sufficient period of time may result in the development of pellagra. Persons with finicky appetites, erroneous dietary habits, and food idiosyncrasies frequently develop pellagra. The handling of such patients calls for great tact, patience, and resourcefulness on the part of the physician. Such persons satisfy their appetite with foods to which they are accustomed and ignore all dietary instruction unless the necessary foods are administered under the supervision of a responsible and intelligent person. The diet of chronic alcoholic addicts should also be supervised carefully. Such persons should be made to take from 3000 to 4000 calories per day if the development of pellagra is to be prevented. They need not necessarily give up drinking so long as they have the money and the appetite to take the required amount of proper foods.

The administration of adequate doses of niacin or niacin amide* or salts that act similarly to persons with pellagra in relapse will relieve them of pellagrous glossitis, stomatitis, vaginitis, urethritis, and proctitis. The administration of these substances is also followed by a disappearance of the erythematous skin lesions of pellagra and a decrease or dis appearance of some of the ether soluble pigments of the urine. These substances also dramatically relieve the person with pellagrous psychosis.

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* The amide of nicotinic acid is to be preferred since its use is not associated with a vasodilator effect of the niacin per se.

Our results over a ten-year study strongly suggest that nicotinic acid or substances that act similarly are essential to the integrity of the cells of the body and that a sufficiently prolonged deficiency of them results in ill health and eventually in pellagra.

The range of dosage is variable. It is effective when injected or given by mouth. We have given as much as 1 Gm. a day for several weeks without injurious effects. We have seen as little as 20 mg. daily effective in some cases. A good average dose is 500 mg. each twenty-four hours.

The physician who wishes to rehabilitate the patient most practically and fully should also recommend mixed vitamin therapy and a diet high in protein and calories such as recommended in Chapter 25.

BIBLIOGRAPHY

1. Boggs, T. R., and Padget, P. Pellagra: analysis of 102 cases. *Bull. Johns Hopkins Hosp.* 50:21, 1932.
2. Elvehjem, C. A., Madden, R. J., Strong, F. M., and Woolley, D. W. The isolation and identification of the anti-black tongue factor. *J. Biol. Chem.* 123:137, 1938.
3. Fouts, P. J., Helmer, O. M., Lepkovsky, S., and Jukes, T. H. Treatment of human pellagra with nicotinic acid. *Proc. Soc. Exper. Biol. & Med.* 37:405, 1937.
4. Funk, C. Studies on beri-beri. VII. Chemistry of the vitamine-fraction from yeast and rice-polishings. *J. Physiol.* 46:173, 1913.
5. Goldberger, J., and Tanner, W. F. A study of the treatment and prevention of pellagra: experiments showing the value of fresh meat and milk, the therapeutic failure of gelatin, and the preventive failure of butter and of cod-liver oil. *Pub. Health Rep.* 39:87, 1924.
6. Goldberger, J., and Tanner, W. F. A study of the pellagra-preventive action of dried beans, casein, dried milk, and brewers' yeast. *Pub. Health Rep.* 40:54, 1925.
7. Goldberger, J., Waring, C. H., and Tanner, W. F. Pellagra prevention by diet among institutional inmates. *Pub. Health Rep.* 38:2361, 1923.
8. Goldberger, J., and Wheeler, G. A. The experimental production of pellagra in human subjects by means of diet. *Hyg. Lab. Bull.* 120:7, 1920.
9. Goldberger, J., and Wheeler, G. A. A study of the pellagra-preventive action of the tomato, carrot, and rutabaga turnip. *Pub. Health Rep.* 42:1299, 1927.
10. Goldberger, J., Wheeler, G. A. Lillie, R. D., and Rogers, L. M. A further study of butter, fresh beef and yeast as pellagra preventives.

with consideration of the relation of factor P-P of pellagra (and black tongue of dogs) to vitamin B. *Pub. Health Rep.* 41:297, 1926.

11. Harris, L. Nicotinic acid and the pellagra-preventing vitamin. *Nature,* 140:1070, 1937.
12. Huber, C. *Ann. d. Chem.* 141:271, 1867.
13. Kuhn, R., and Vetter, H. Isolierung von Nicotinsäure-amid aus Herzmuskel. *Ber. d. deutsch. chem. Gesellsch.* 68:2374, 1935.
14. Smith, D. T., Ruffin, J. M., and Smith, S. G. Pellagra successfully treated with nicotinic acid: a case report. *J.A.M.A.* 109:2054, 1937.
15. Spies, T. D. Treatment of pellagra by means of parenteral liver extract. *Proc. Soc. Exper. Biol. & Med.* 31:363, 1933.
16. Spies, T. D. The treatment of pellagra. *J.A.M.A.* 104:1377, 1935.
17. Spies, T. D., Cooper, C., and Blankenhorn, M. A. The use of nicotinic acid in the treatment of pellagra. *J.A.M.A.* 110:622, 1938.
18. Spies, T. D., and DeWolf, H. F. Observations on the etiological relationship of severe alcoholism and pellagra. *Am. J. M. Sc.* 186:521, 1933.
19. Suzuki, U., Shimamura, T., and Odake, S. Über Oryzanin, ein Bestandteil der Reiskleie und seine physiologische Bedeutung. *Biochem. Ztschr.* 43:89, 1912.
20. Vickery, H. B. Simpler nitrogenous constituents of yeast. I. Choline and nicotinic acid. *J. Biol. Chem.* 68:585, 1926.
21. Warburg, O., and Christian, W. Co-ferment problem. *Biochem. Ztschr.* 275:464, 1935.
22. Wheeler, G. A. The pellagra-preventive value of canned spinach, canned turnip greens, mature onions, and canned green beans. *Pub. Health Rep.* 46:2663, 1931.
23. Wheeler, G. A. The pellagra-preventive value of autoclaved dried yeast, canned flaked haddock, and canned green peas. *Pub. Health Rep.* 48:67, 1933.
24. Wheeler, G. A., and Hunt, D. J. The pellagra-preventive value of green cabbage, collards, mustard greens, and kale. *Pub. Health Rep.* 48:754, 1933.
25. Wheeler, G. A., and Sebrell, W. H. The control of pellagra. *J.A.M.A.* 99:95, 1932.
26. Williams, R. R. Structure of antineuritic hydroxy pyridines. *Proc. Soc. Exper. Biol. & Med.* 14:25, 1916.
27. Williams, R. R. The chemical nature of the "vitamines." I. Antineuritic properties of the hydroxypyridines. *J. Biol. Chem.* 25:437, 1916.

Chapter 21

THE PTEROYLGLUTAMATES IN NUTRITION

William J. Darby and Edgar Jones

CONSIDERABLE interest centers about the activity of the group of vitamins which are variously known as the pteroylglutamates, "folic acid," "vitamin M," or *L. casei* factors. The reader is referred to several reviews for an extensive development of the history of these substances (Day,[16] Day and Totter,[21] Pfiffner and Hogan,[44] Berry and Spies,[5] Darby,[10] Stokstad and Hutchings,[54] Jukes and Stokstad.[30]) It suffices to note here the following landmarks in the development of knowledge in this field:

McCarrison[33] observed in 1921 the occurrence in monkeys of anemia and diarrhea when they were maintained on a diet deficient in "vitamin B."

In 1934 Wills[68] demonstrated that a deficiency of a vitamin was the cause of tropical macrocytic anemia and differentiated the factor from the anti-pernicious-anemia substance present in purified liver extract.[69]

Day, Langston, and Shukers (1935) independently described anemia, leukopenia, diarrhea, and oral lesions in monkeys as a deficiency syndrome which was later attributed to a lack of vitamin M.[17] This syndrome was not prevented by purified anti-pernicious-anemia liver extracts.[18, 32]

The chick was found to require a new dietary factor for growth (factor U)[56] and prevention of anemia (vitamin B_c).[27] Crystalline B_c from liver possessed hemopoietic activity for the chick[42] and later proved to be identical with pteroylglutamic acid. Concentrated anti-pernicious-anemia liver extract was inactive for the B_c-deficient chick.[41]

The existence of an unidentified growth factor for *L. casei* was reported by Snell and Peterson.[50] Mitchell, Snell, and Williams[36] termed a similar microbiologic growth factor "folic acid."

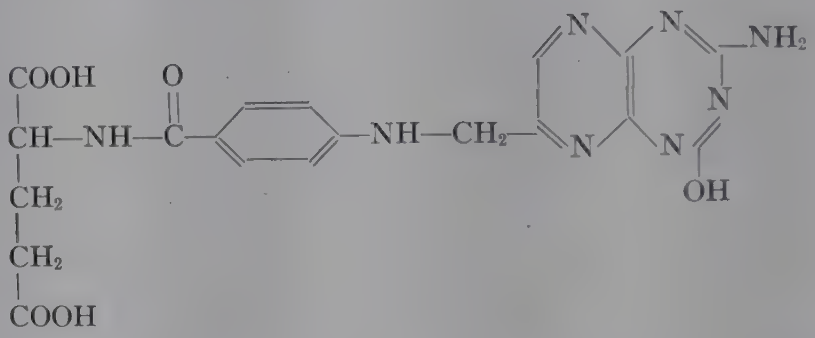
Day *et al.*[20] demonstrated the activity of an isolated (liver) *L. casei* factor in vitamin-M-deficient monkeys.

The synthesis and structure of *L. casei* factor was announced (Angier et al.[2, 3]) and the structure of B_c and B_c-conjugate related thereto (Pfiffner *et al.*[43]).

The hemopoietic activity of synthetic pteroylglutamic acid in sprue,[11] unclassified macrocytic anemia,[51] pernicious anemia,[37, 62] pernicious anemia of pregnancy,[37] and nutritional macrocytic anemia[62] was reported.

CHEMISTRY

Pteroylglutamic acid is the simplest member of this group of vitamins. It is a yellow compound sparingly soluble in water. The structure is indicated by the following formula.[3]



It is noted that the molecule contains a pterin, para-aminobenzoic acid, and glutamic acid. The moiety consisting of the pterin and *p*-aminobenzoic acid is known as pteroic acid, the corresponding acyl radical as the pteroyl radical. Two other pteroylglutamates occur in nature: the triglutamate ("fermentation factor") and the heptaglutamate (B_c-conjugate). These possess three and seven glutamic residues respectively linked by gamma peptide chains to the pteroyl moiety. The triglutamate has been synthesized ("Teropterin"). The heptaglutamate is present in yeast. A synthetic diglutamate ("Diopterin") has also been prepared.

Chemical methods for the determination of these substances in body fluids have not yet been developed. Microbiologic methods of assay are available and permit differentiation of certain of the glutamates.[57] Such determinations have not yet proved of diagnostic value.

PHYSIOLOGY

Pteroylglutamic acid (PGA) is active in man following oral, parenteral, or rectal administration. The exact mechanism and site of absorption is unknown. It is usually excreted in but small amounts in the urine and as free PGA. Thus, employing S. *faecalis* as the test organism, Johnson, Hamilton, and Mitchell[29] found an average twenty-four-hour urinary excretion of 8 micrograms of folic acid, while Steinkamp *et al.*[52] found an excretion of 2.34 ± 1.08 micrograms in twenty-four hours. Values similar to the latter were found by Swendseid *et al.*[59] who employed *L. casei* as the test organism. From 20 to 30 per cent of single oral test doses of PGA is excreted in the urine from about two to eight hours after ingestion.[52, 59] The ratio of dermal loss to urinary loss of folic acid is high, apparently 5 or 6.[29]

Hospitalized patients excreted considerably less of a single oral test dose than did healthy adults, a finding consistent with the interpretation that these patients were "unsaturated."[52]

The administration of the heptaglutamate to healthy persons was followed by the urinary excretion of free PGA.[59] The conversion of the conjugate to the free monoglutamate is due to the activity of an enzyme known as conjugase. Accompanying the conjugate in some crude products is an undefined inhibitor of the conjugase. When this inhibitor is ingested simultaneously with the heptaglutamate there is a pronounced reduction in the urinary excretion of the free PGA.[59] This observation indicates that the conjugase inhibitor renders the conjugate unavailable. It has been suggested[6] that the intrinsic factor of Castle may act as an anti-conjugase-inhibitor.

Pteroylglutamic acid has been found to exert a remarkable hemopoietic effect in a number of macrocytic anemias which are characterized by megaloblastic arrest of the marrow. In addition, this vitamin favorably influences gastrointestinal function in sprue. The detailed mechanism of these actions is unknown at present. PGA does not protect the subject with pernicious anemia against the development of peripheral neuritis and spinal cord changes.

The hemopoietic activity of PGA has been demonstrated in sprue, pernicious anemia, nutritional macrocytic anemia, the macrocytic anemia associated with pellagra, pernicious anemia of pregnancy, and tropical macrocytic anemia. It is not active in the macrocytic anemia of cirrhosis of the liver or in the liver-refractory anemias. This last statement requires some qualification as cases have been reported of patients with so-called achrestic anemia who were refractory to liver extract yet who exhibited a hemopoietic response to PGA.[64] The complete study of such unusual cases should give a better insight into the mode of action of various hemopoietic agents.

The hemopoietic activity of purified anti-pernicious-anemia liver extract is not due to PGA—in fact, the "folic acid" content of most purified liver extracts is negligible,[9] and potent anti-pernicious-anemia liver extract is devoid of hemopoietic activity for the deficient monkey[18] or chick.[41, 55] Chemically, the active fraction of liver extract seems to be distinct from the pteroylglutamates.[58] That the two factors possess different activities in man will be evident from the ensuing discussion.

Available data which permitted a quantitative comparison of the hemopoietic responses initiated by liver extract and by PGA have been summarized elsewhere by one of the writers.[10] Inclusion of reports which have appeared since that compilation does not materially alter the conclusions reached at that time. These may be summarized as follows:

The *reticulocyte maximum* in patients with pernicious anemia occurred within the same period of time following the two therapeutic agents. After oral PGA, the reticulocyte maximum was slightly higher than following parenterally administered PGA. Oral PGA resulted in reticulocytoses higher than that produced by oral liver, but parenteral PGA promoted somewhat lower reticulocyte responses than did parenteral liver extract.

The rate of *erythrocyte regeneration* after either oral or parenteral PGA was slower than the standards for patients adequately treated with liver extract. The erythrocyte increase following therapy with PGA may continue for a period of up to three months.

The maximum erythrocyte count and hemoglobin level which is obtained in most cases of pernicious anemia following treatment with PGA is similar to the maximum reached after therapy with liver extract. In some cases, these levels have not been maintained by pteroylglutamic acid alone.

Reticulocyte and erythrocyte increases are accompanied by hemoglobin regeneration, reduction in the macrocytosis, increased leucocyte count, and (temporarily) a greatly increased number of platelets. The bone marrow changes from the hyperplastic megaloblastic type characteristic of these anemias to normoblastic and finally to normal.

The rare patient may exhibit little or no hematologic response to PGA but subsequently respond to liver extract.[64] In other patients, PGA may induce good initial hematologic remissions but with a subsequent relapse despite continuous treatment with the factor. The patients will then respond to liver extract. Three such experiences have been encountered among the patients at Vanderbilt who have been continued on PGA.

In sprue the erythrogenic activity of PGA appears to be identical in character with that of liver extract. Long-term observations have not appeared on the effect of PGA in sprue, but it seems that true hematologic relapses during active therapy with PGA have been rare. Quantitative comparisons of the responses to PGA and to liver extract are not possible yet in nutritional macrocytic anemia, macrocytic anemia of pregnancy, and tropical macrocytic anemia.[13] The cases reported to date, however, indicate excellent hematologic response to this agent.

It seems that those macrocytic anemias which are often associated with a diet of poor quality and which may, therefore, more nearly approach true deficiency disease (in contrast to the metabolic disorder which results in pernicious anemia), respond especially well to this vitamin. Taken together with the essential nature of the vitamin for hemopoiesis in many species of animals (monkey, chick, rat, turkey, fox, mink, and guinea pig[40]) it is apparent that this substance plays an essential role in hemopoiesis. An experimental deficiency of pteroylglutamates has not yet been produced in man, so it is not possible to conclude that this species normally requires the factor. It would be surprising, however, if it were proved that man did not have a dietary need for the vitamin.

Another physiologic effect of the pteroylglutamates has to do with its influence on the gastrointestinal tract. McCarrison[33] wrote that in "vitamin B deficient" monkeys, "The diarrhoeic motions were small, numerous and pale in colour. . . . In animals receiving butter in addition to the autoclaved rice . . . large amounts of fatty acids were present (in the stools). In such cases, the stools were paler than usual, and in two instances distinctly frothy, resembling those of sprue, the resemblance being carried further by their high fatty acid content." Day, Langston, and Shukers[19] observed oral lesions and diarrhea in their deficient monkeys and, later, Langston, Darby, Shukers, and Day[32] included these signs as part of the syndrome of vitamin M deficiency. Diarrhea and oral lesions are also observed in rats receiving an antagonist to pteroylglutamic acid.[22]

Diarrhea is very common in sprue and is characterized by increased lipid content of the stools. Chemical studies indicate that there is malabsorption from the gastrointestinal tract of fat, fat-soluble vitamins, glucose, calcium, and possibly other nutrients.[26, 60] X-ray evidences of altered tone and motility of the small intestine probably reflect damage to the intramural nerve plexuses in sprue.[24] These evidences of gastrointestinal malfunction in sprue are usually partially or completely reversible by liver extracts, and this has been widely interpreted as evidence of their deficiency nature. In some cases, the gastrointestinal changes may have reached an irreversible phase.[25] In other cases, the deficiency disease may develop secondarily to abnormalities of gastrointestinal function, as in celiac disease.[1]

The treatment of sprue with PGA has usually been followed by alleviation of the diarrhea and glossitis, by a gain in weight, return toward normal of the glucose tolerance curve, and an increase in the concentration of fat-soluble vitamins in the blood.[12] Roentgenologic studies of the gastrointestinal tract have revealed a return toward normal following therapy with PGA.[4, 12] Less complete responses have been observed in cases of long standing, an observation consistent with the possible occurrence of irreparable damage in these cases, such as has been experienced in treating some patients with liver extract.

These various observations indicate that pteroylglutamic acid is involved in some manner in the maintenance of normal gastrointestinal function, particularly absorption.

In lower species other physiologic functions of the pteroylglutamates have been described. Thus, they are essential for normal feathering in the chick, for oviduct growth under the stimulus of stilbestrol, for prevention of a cervical paralysis in turkeys, for maintenance of resistance of monkeys to infection with *B. dysenteriae*[28] or *Streptococcus hemolyticus* (group C),[48] for oxidation of tyrosine by rats[46] and guinea pigs[71] as well as for growth of numerous microorganisms,[30] for the synthesis of thymine and adenine by S. *faecalis R*,[57] and of porphyrin production by *Corynebacterium hoffmannii.*[61]

PTEROYLGLUTAMATE DEFICIENCY IN MAN

The syndromes which respond to pteroylglutamic acid are characterized by the common findings of macrocytic anemia and glossitis. The macrocytic anemia is accompanied by megaloblastic arrest in the marrow. These syndromes are usually characterized further by varying degrees of gastrointestinal malfunction—diarrhea, steatorrhea, malabsorption—which are least marked in pernicious anemia. Except in cases of pernicious anemia, the dietary histories usually (but not invariably) reveal a low intake of animal protein and green vegetables and fruits. Except for pernicious anemia, the diseases are most frequently encountered in warmer regions but are not absent from northern temperate zones. They may recur during periods of stress, especially during pregnancy. It is difficult to separate these syndromes categorically and it may be that, except for pernicious anemia, they are etiologically the same and that the usual distinctions are one of degree or of time of occurrence. Pernicious anemia, however, would seem to be set apart from the others of this group by the following points: constant, irreversible, histamine-refractory achlorhydria;

the much more frequent appearance of neurologic disturbances; the consistent absence of Castle's intrinsic gastric factor; disassociation from poor dietary; less remarkable absorptive difficulties and absence of steatorrhea; and geographical distribution.

These considerations are compatible with the concept that pernicious anemia is etiologically separate from the remainder of the group of anemias and is due to the metabolic defect (absence of Castle's factor) in the subject. The remainder of the group—sprue, pellagra, nutritional macrocytic anemia, tropical macrocytic anemia, macrocytic anemia of pregnancy, and megaloblastic anemia of infants—may more nearly approach true deficiency states. It is impossible to assign the relative roles of dietary inadequacy, changes in the gastrointestinal flora, unrecognized gastrointestinal lesions, constitutional factors, parasitic infestations, and other factors in the pathogenesis of these anemias. Andersen[1] holds that the macrocytic anemia and steatorrhea which accompanies celiac disease is comparable to rickets or scurvy accompanying the same disease—that it is a deficiency state superimposed upon a basic constitutional disease. It may be that a similar pathogenesis accounts for other syndromes of this group.

It is beyond the scope of this chapter to discuss in detail the clinical picture of these various anemias. The following brief descriptions will suffice to define the syndromes as discussed here and the reader is referred to the several excellent reviews cited for detailed descriptions of each disease entity.

Pernicious anemia is characterized by a macrocytic anemia* with hyperplastic megaloblastic bone marrow, a histamine-refractory achlorhydria, glossitis, and, frequently, neurologic changes from peripheral neuritis to degenerative lesions which may involve either the posterior or lateral columns of the spinal cord or both. The physical signs which may be encountered are impaired vibratory sense, ataxia, positive Romberg sign, loss of position sense, Babinski's sign, spasticity, hypo- or hyperactive reflexes, clonus, and loss of sphincter control. These may occur with or without pronounced anemia. Although diarrhea may be encountered, there is no steatorrhea and the glucose and vitamin A tolerance curves are not flat.

Sprue[26] is often divided into tropical and nontropical. We consider that the two are identical and that one should differentiate the complete pic-

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* *Macrocytic* is usually defined as a mean corpuscular volume (MCV) of greater than 95 cubic micra:

$$\text{MCV} = \frac{\text{Volume of packed red cells (\%)} \times 10}{\text{Erythrocyte count in millions}}$$

The division between normocytic and macrocytic is not absolute, however, as an MCV greater than 95 may occasionally be met in a healthy individual.

ture of sprue from the so-called idiopathic steatorrheas which are not infrequently encountered and most often are not accompanied by anemia. Sprue is characterized by glossitis, diarrhea with increased fat in stools, a macrocytic anemia with leukopenia and thrombopenia, a megaloblastic bone marrow, usually much weight loss, pigmentation of the skin, usually a low blood pressure, a flat oral glucose tolerance curve with a normal intravenous glucose tolerance curve, impaired absorption of fat-soluble vitamins, a low serum carotene level, and a "deficiency" pattern of the small intestine following a barium meal. Castle's intrinsic factor may be present or absent.

Nutritional macrocytic anemia is a syndrome of macrocytic anemia, with megaloblastic bone marrow, inconstant glossitis, diarrhea, and absorptive defects. Neurologic involvement is rare. Castle's intrinsic factor is present. The syndrome is most often encountered in malnourished persons and may accompany pellagra. It is difficult to distinguish this syndrome from tropical macrocytic anemia.

Pernicious anemia of pregnancy[8, 65, 70] is a macrocytic anemia which has its onset during the last trimester of pregnancy or shortly postpartum. Achlorhydria is the exception. The bone marrow is megaloblastic. Glossitis and gastrointestinal disturbances (vomiting, indigestion, diarrhea) are common. Neurologic involvement is rare. The response to anti-pernicious-anemia liver concentrates is variable but the cruder preparations are usually effective.[65]

Megaloblastic anemia of infancy[72] is encountered in infants from two to sixteen or twenty months of age. Macrocytic anemia, leukopenia, and thrombopenia accompanied by megaloblastic marrow is found. Histamine-refractory achlorhydria is usual. The deficiency is not a permanent one (in contrast to pernicious anemia) and the etiology is not clear, although a dietary deficiency has been suspected.

The most useful laboratory measures in conjunction with a study of these anemias are accurate hematologic data including red cell counts, hemoglobin concentration (in grams), and packed cell volume (hematocrit readings), leukocyte counts, differential count and study of blood smear, and a study of bone marrow. These data permit morphologic classification of the anemia and separation from most other anemias such as that of iron deficiency, that due to hemolysis, and myelophthisic anemia. Gastric analysis following histamine injection permits the detection of true achlorhydria. Estimation of fecal fat in a twenty-four-hour stool specimen may reveal steatorrhea, but a preferred method is to determine lipid balance during a collection of longer duration (four to twelve days). An estimated absorption of less than 90 per cent of ingested fat under these conditions may be regarded as steatorrhea. Simultaneous determinations of fecal nitrogen loss permit an evaluation of pancreatic function. Serum carotene levels, which fluctuate more rapidly than do vitamin A levels, may, if low, indicate impaired absorption of fat-soluble materials. Vitamin A tolerance curves are of value in detecting abnormalities of fat absorption. Similarly, prothrombin concentrations are useful for measuring vitamin K. X-ray studies of the stomach and small intestine assist in differentiation of deficiency states from steatorrheas resulting from intrinsic gastrointestinal defects.

TREATMENT

Therapeutically, pteroylglutamic acid is probably of greatest value in those syndromes discussed above which more nearly approach deficiency diseases—nutritional macrocytic anemia, sprue, pernicious anemia of pregnancy, megaloblastic anemia of infancy and probably, tropical macrocytic anemia. Inasmuch as it does *not* protect against the subsequent development of neurologic disease in pernicious anemia and a limited number of cases either fail to respond hematologically or may respond initially and then suffer a hematologic relapse, *PGA alone* is not a dependable therapeutic agent in this disease.

Claims have been made of advantages to therapy of pernicious anemia with a combination of liver extract and PGA.[35] The reported cases are too few to evaluate such a treatment regimen at present, but it appears probable to the writers that any such advantage may be restricted to those rare patients who fail to respond hematologically to potent liver but do improve after receiving PGA. Clinically these represent an entity which probably should not be classified as pernicious anemia. Inasmuch as there are some reports of better gastrointestinal effects in sprue following treatment with PGA than with liver extract alone,[14, 63] it may be useful to employ a combination of the two agents in sprue or the similar syndromes which exhibit gastrointestinal disturbances and anemia if they respond incompletely to one agent.

Pteroylglutamic acid has been reported to be effective in some cases of "aplastic anemia,"[23] in anemia associated with rheumatoid arthritis,[53] in agranulocytosis,[7] in granulocytopenia following sulfonamide therapy,[34] in megaloblastic anemia after total gastrectomy,[39] and in bone marrow depression after X-ray therapy.[15, 66] These are sporadic reports and require confirmation and further study before one can evaluate the therapeutic usefulness of PGA in such conditions. A listing of diseases in which PGA has been reported to be ineffective was compiled by Jukes and Stokstad[30] and includes macrocytic anemia accompanying cirrhosis of the liver, the anemia of prematurity, iron deficiency anemia (hypochromic microcytic anemia), sickle cell anemia, Mediterranean anemia, and a variety of leukemias.

The effective therapeutic doses of PGA which have been employed in treatment of these anemias have varied from 0.5 to 120 mg. daily, administered either orally or parenterally. The daily dosage range of 5-20 mg. daily appears to be as consistently effective as larger amounts and is therefore to be recommended. These quantities may be given by oral, intramuscular, or intravenous routes. It is premature to discuss the use of the triglutamate or heptaglutamate, but the minimal effective dosages of these seem to be greater than for the monoglutamate.

As stated above, PGA alone is not adequate therapy for patients with pernicious anemia. Intramuscular liver extract continues as a satisfactory method of maintenance for such patients. It has been suggested that combined therapy with PGA and liver extract provide greater hematologic effect than either agent alone[35, 47] but this suggestion requires further evaluation. The suggestion that PGA may unfavorably alter the metabolism of the nervous system and thereby precipitate neurologic disease has been made by Ross and his co-workers,[47] but seems unlikely inasmuch as it is actually a vitamin necessary for the prevention of a paralysis in the turkey.[31] If the patient is emaciated or wasted it is desirable in addition to specific therapy to place him on a regimen of four to six liberal meals daily, especially abundant in good quality protein such as lean meats, eggs, and milk, until body weight and hematologic values are restored. In sprue the hemorrhagic tendency due to hypoprothrombinemia should be treated by parenterally administered preparation of vitamin K or a water-soluble vitamin K orally. Low-calcium tetany which is occasionally encountered may be alleviated by a parenteral calcium preparation and followed by a potent vitamin D supplement (preferably water-dispersible) coupled with a good intake of dietary calcium and a low-fat diet. If diarrhea is obstinate in sprue it is well to decrease the fat content of the diet until the symptom has been brought under control. Since the dietaries of the patients are often of poor quality, it is important to reeducate the patient as to his eating habits. This usually involves an effort to increase the intake of fruits, green vegetables, and lean meat. Alcohol should be permitted only in moderation, as patients with sprue tend to suffer gastrointestinal exacerbations after excessive drinking. Unless chronic blood loss or parasitic infestation has preceded the development of the macrocytic anemia, there is no need for supplementary iron.

Pernicious anemia and sprue show pronounced tendencies to relapse, hence continuous specific maintenance therapy is required by the patient with pernicious anemia and by most patients with sprue. Some sprue victims may maintain themselves after a remission on a good dietary alone. Persons with nutritional macrocytic anemia likewise may relapse unless specific therapy is continued or drastic dietary changes are instituted. The patient with pernicious anemia of pregnancy appears to have a tendency to relapse with subsequent pregnancies but does not require continuous specific therapy to maintain a remission. The megaloblastic anemia of infants shows no tendency to relapse. Maintenance dosages of 5 mg. of PGA daily by mouth seem adequate where needed. If relapse occurs at such a dosage level it has been our experience that larger quantities have not produced remissions and that a deficiency of some other factor has developed.

RELATED HEMOPOIETIC AGENTS

Two other hemopoietic agents should be mentioned in conjunction with the pteroylglutamates, although neither are members of this group of factors. Thymine (5-methyl-uracil, not to be confused with thiamine) possesses hemopoietic activity in the macrocytic anemias if administered in very large quantities. This effect is of considerable scientific interest but is of "no practical therapeutic value at the dosage level required . . ."

In April, 1948, the isolation from liver of a red crystalline material which was hemopoietically active in pernicious anemia was announced[45] from the Merck Laboratories. West[67] showed that this material was effective in the treatment of pernicious anemia in relapse. Parenteral administration of a few micrograms was found to give good reticulocyte responses and to be followed by appreciable increases in red blood cells and hemoglobin. It was reported by Shorb[48a] that this material served as an essential growth factor for *Lactobacillus lactis Dorner,* which activity led to the microbiologic designation of LLD factor. It was further demonstrated that there is an essentially linear relationship between LLD activity of liver extracts and their anti-anemic potency. The material has since been designated as vitamin B_{12}. Its structure is unknown, but it has been found to contain cobalt, phosphorus, and nitrogen and to have a molecular weight of approximately 1600.

Simultaneously with the announcement from the Merck Laboratories, Smith[49] of England described two red pigments highly active in pernicious anemia and isolated from ox liver. The more potent material was obtained from proteolyzed liver and was purified by partition chromatography. Doses of the order of 0.3 mg. of concentrate were effective in patients with pernicious anemia during relapse. The clinical efficacy of these pigments appeared to be directly related to their color intensity. It was realized that these preparations used by the British workers were not pure. No case reports were presented in the original publications on these pigments, but it was stated that they were "effective" in 3 cases of pernicious anemia with subacute combined degeneration of the spinal cord. Subsequent reports[4b] from this country have also indicated that vitamin B_{12} is effective in those patients with pernicious anemia having neurologic manifestations. The materials isolated by Smith were very soluble in water, but insoluble in ether or in chloroform. It was concluded that Smith was dealing with two differing forms of the liver factor effective in pernicious anemia, and suggested that only this one factor is required for both the hematologic and neurologic aspects of the disease.

Spies and collaborators,[51a, b] in short-term observations, have confirmed the efficacy of this material in the treatment of pernicious anemia, and have also indicated that it is active hemopoietically in both sprue and nutritional macrocytic anemia. On the other hand, a case of macrocytic anemia of pregnancy has been reported by Bethell and others[6a] in which there was no hematologic response to vitamin B_{12}, but an excellent subsequent response to pteroylglutamic acid. There are several reports in the literature, confirmed by the personal experience of the authors with 3 such patients, to indicate that patients showing various sensitivity reactions following injection of liver extract show no such reaction following administration of vitamin B_{12}.

The first quantities of this new vitamin were obtained by isolation from liver, but subsequently other sources have been described. Among these sources are beef extract, milk powder, and the culture media of several micro-organisms. Of particular interest is the finding that *Streptomyces griseus* is a source of vitamin B_{12}.

Castle and co-workers[4a] have announced that normal gastric juice enhances greatly the potency of orally administered crystalline vitamin B_{12}. Thus, it would appear that this material can serve as extrinsic factor. This report has since been confirmed by Hall, Morgan, and Campbell.[24a] Inasmuch as vitamin B_{12} is effective in the treatment of pernicious anemia when given alone by parenteral injection, the enhancement of the orally given vitamin by the simultaneous administration of normal gastric juice leads to the suggestion that perhaps a function of the "intrinsic factor" contained in normal gastric juice is to promote the absorption and possibly the utilization of vitamin B_{12}. Another plausible interpretation is that the intrinsic factor serves to protect the orally administered vitamin from inactivation.

We have shown[29a] that in patients with pernicious anemia in relapse decreases in fecal urobilinogen occurred following treatment with vitamin B_{12}. This vitamin does not affect the urinary excretion of pteroylglutamic acid in pernicious anemia and in sprue.

From personal observation it would appear that at least one microgram daily of this vitamin is required for satisfactory hemopoiesis. However, when 1 microgram of crystalline material was given by injection daily for twenty-two consecutive days to a patient with pernicious anemia an optimal reticulocyte response followed by a sharp rise in red blood cells and hemoglobin followed, this rise being halted abruptly when therapy was discontinued. This can be taken to mean that 1 microgram per day was sufficient for optimal hemopoiesis, but permitted no storage of the vitamin. Other unpublished studies may be interpreted as indicating that a daily parenteral dose of 3 micrograms is more consistently accompanied by satisfactory erythropoiesis. Up to the present time, no reports have been published to indicate that this material is effective when given alone by mouth. We have, however, observed a remission in a patient as a result of therapy with 60 micrograms of B_{12} orally without gastric juice supplement.

It is of interest that a reticulocyte response was obtained following the administration of vitamin B_{12} to a patient with sprue who had undergone hematologic relapse while receiving previously adequate amounts of PGA by mouth.

Any expression at this time of a satisfactory clinical dosage schedule with vitamin B_{12} must be regarded as tentative. However, inasmuch as the evidence indicates that, as a first approximation, one microgram of the vitamin is equivalent to one unit or slightly less of liver extract, it is reasonable to predict that the following schedule may prove satisfactory: initial parenteral therapy sufficient to provide 200 to 300 micrograms of B_{12} within the first two to four weeks, followed by maintenance therapy of 20 to 40 micrograms per month.

Vitamin B_{12}, in doses of a few micrograms, has proved efficacious in the treatment of certain instances of megaloblastic anemia of infants. Other cases of this syndrome have failed to respond to this agent but subsequently have responded well to administration of pteroylglutamic acid.[71a] The present experience indicates, therefore, that B_{12} is less frequently effective in this condition of infants than is folic acid. There is no manner at present which permits the differentiation of those infants who are refractory to vitamin B_{12} from those who respond.

BIBLIOGRAPHY

1. Andersen, D. H. Celiac syndrome, VI. *J. Pediat.* 30:564, 1947.
2. Angier, R. B., *et al.* Synthesis of a compound identical with the *L. casei* factor isolated from liver. *Science* 102:227, 1945.
3. Angier, R. B., *et al.* The structure and synthesis of the liver *L. casei* factor. *Science* 103:667, 1946.

4. Beguerie, R. L. H., and Spies, T. D. Roentgenologic studies on the effect of synthetic folic acid on the gastrointestinal tract of patients with tropical sprue. *Am. J. Roentgenol.* 56:337, 1946.

4a. Berk, L., Castle, W. B., Welch, A. D., Heinle, R. W., Anker, R., and Epstein, M. Observations on the etiologic relationship of achylia gastrica to pernicious anemia. X. Activity of vitamin B_{12} as food (extrinsic) factor, *New England J. Med.* 239:911, 1948.

4b. Berk, L., Denny-Brown, D., Finland, M., and Castle, W. B. Effectiveness of vitamin B_{12} in combined system disease, rapid regression of neurologic manifestations and absence of allergic reactions in a patient sensitive to injectable liver extracts. *New England J. Med.*, 239:328, 1948.

5. Berry, L. J., and Spies, T. D. The present status of folic acid. *Blood* 1:271, 1946.

6. Bethell, F. H., Meyers, M. C., Andrews, G. A., Swendseid, M. E., Bird, O. D., and Brown, R. A. Metabolic function of pteroylglutamic acid and its hexaglutamyl conjugate. *J. Lab. & Clin. Med.* 32:3, 1947.

6a. Bethell, F. H. Meyers, M. C., Neligh, R. B. Vitamin B_{12} in pernicious anemia and puerperal macrocytic anemia. *J. Lab. & Clin. Med.*, 33:1477, 1948.

7. Black, D. A. K., and Stanbury, S. W. Folic acid in agranulocytosis. *Lancet* 1:827, 1947.

8. Callender, S. T. E. A critical review of pernicious anemia of pregnancy. *Quart. J. Med.* 13:75, 1944.

9. Clark, G. W. Vitamin content of liver extracts for parenteral use. *Am. J. Med. Sci.* 209:520, 1945.

10. Darby, W. J. The physiological effects of the pteroylglutamates in man —with particular reference to pteroylglutamic acid (PGA). *Vitamins and Hormones* 5:119, 1947.

11. Darby, W. J., and Jones, E. Treatment of sprue with synthetic *L. casei* factor (folic acid, vitamin M). *Proc. Soc. Exper. Biol. & Med.* 60:259, 1945.

12. Darby, W. J., Jones, E., Warden, H. F., and Kaser, M. M. The influence of pteroylglutamic acid (a member of the vitamin M group) on gastrointestinal defects in sprue: A study of the interrelationships of dietary essentials. *J. Nutrition* 34:645, 1947.

13. Das Gupta, C. R., and Chatterjea, J. B. The role of synthetic folic acid (*L. casei* factor) in the treatment of nutritional macrocytic anemia. *Indian Med. Gaz.* 81:402, 1946.

14. Davidson, L. S. P., and Girdwood, R. H. Folic acid as a therapeutic agent. *Brit. M. J.* 1:587, 1947.

15. Davis, P. L. Folic acid and the bone marrow in radiation therapy. *Am. J. Med.* 1:634, 1946.

16. Day, P. L. The nutritional requirements of primates other than man. *Vitamins and Hormones* 2:71, 1944.

17. Day, P. L., Langston, W. C., and Darby, W. J. Failure of nicotinic acid to prevent nutritional cytopenia in the monkey. *Proc. Soc. Exper. Biol. & Med.* 38:860, 1938.

18. Day, P. L., Langston, W. C., Darby, W. J., Wahlin, J. G., and Mims, V. Nutritional cytopenia in monkeys receiving the Goldberger diet. *J. Exper. Med.* 72:463, 1940.

19. Day, P. L., Langston, W. C., and Shukers, C. F. Leucopenia and anemia in the monkey resulting from vitamin deficiency. *J. Nutrition* 9:637, 1935.

20. Day, P. L., Mims, V., Totter, J. R., Stokstad, E. L. R., Hutchings, B. L., and Sloane, N. H. The successful treatment of vitamin M deficiency in the monkey with highly purified *Lactobacillus casei* factor. *J. Biol. Chem.* 157: 423, 1945.

21. Day, P. L., and Totter, J. R. The bioassay of the vitamin M group. *Biol. Symposia* 12:313, 1947.

22. Franklin, A. L., Stokstad, E. L. R., Belt, M., and Jukes, T. H. Biochemical experiments with a synthetic preparation having an action antagonistic to that of pteroylglutamic acid. *J. Biol. Chem.* 169:427, 1947.

23. Gendel, B. R. Folic acid in the treatment of aplastic anemia. *J. Lab. & Clin. Med.* 32:139, 1947.

24. Golden, R. Radiologic Examination of the Small Intestine. Philadelphia, Lippincott, 1945.

24a. Hall, B. E., Morgan, E. H., and Campbell, D. C. Oral administration of vitamin B_{12} in pernicious anemia. I. Presence of intrinsic factor in Berkefeld-filtered pooled human gastric juice: Preliminary report. *Proc. Staff Meet. Mayo Clin.* 24:99, 1949.

25. Hanes, F. M. Diagnostic criteria and resistance to therapy in the sprue syndrome. *Am. J. M. Sc.* 204:436, 1942.

26. Hanes, F. M. Sprue. *Tice's Practice of Medicine,* IV:171, 1946.

27. Hogan, A. G., and Parrott, E. M. Anemia in chicks due to vitamin deficiency. *J. Biol. Chem.* 128:46, 1939.

28. Janota, M., and Dack, G. M. Bacillary dysentery developing in monkeys on a "vitamin M" deficient diet. *J. Infect. Dis.* 65:219, 1939.

29. Johnson, B. C., Hamilton, T. S., and Mitchell, H. H. The excretion of "folic acid" through skin and in the urine of normal individuals. *J. Biol. Chem.* 159:425, 1945.

29a. Jones, E., Darby, W. J., Totter, J. R. Pernicious anemia and related anemias treated with vitamin B_{12}. *Blood,* in press.

30. Jukes, T. H., and Stokstad, E. L. R. Pteroylglutamic acid and related compounds. *Physiol. Rev.* 28:51, 1948.

31. Jukes, T. H., Stokstad, E. L. R., and Belt, M. Deficiencies of certain vitamins as studied with turkey poults on a purified diet. *J. Nutrition* 33:1, 1947.

32. Langston, W. C., Darby, W. J., Shukers, C. F., and Day, P. L. Nutritional cytopenia (vitamin M deficiency) in the monkey. *J. Exper. Med.* 68:923, 1938.

33. McCarrison, R. Studies in Deficiency Disease. London, Henry Frowde and Hodder and Stoughton (Reproduced by photo-lithography, Lee Foundation for Nutritional Research, 1945), 1921.

34. Menten, M. L., and Graff, E. Blood changes related to sulfonamide therapy. *Am. J. M. Sc.* 211:672, 1946.

35. Meyer, L. M. Folic acid in the treatment of pernicious anemia. *Blood* 2:50, 1947.

36. Mitchell, H. K., Snell, E. E., and Williams, R. J. The concentration of "folic acid." *J. Am. Chem. Soc.* 63:2284, 1941.

37. Moore, C. V., Bierbaum, O. S., Welch, A. D., and Wright, L. D. The activity of synthetic *Lactobacillus casei* factor ("folic acid") as an anti-pernicious anemia substance. *J. Lab. & Clin. Med.* 30:1056, 1945.

38. Moore, C. V., Vilter, R., Minnich, V., and Spies, T. D. Nutritional macrocytic anemia in patients with pellagra or deficiency of vitamin B complex. *J. Lab. & Clin. Med.* 29:1226, 1944.

39. Morgans, M. E., Rimington, C., and Whittaker, N. Folic acid in megaloblastic anemia after total gastrectomy. *Lancet* 2:128, 1947.

40. *Nutrition Reviews.* The present knowledge of pteroylglutamates. 6:131, 1948.

41. O'Dell, B. L., and Hogan, A. G. Additional observations on the chick antianemia vitamin. *J. Biol. Chem.* 149:323, 1943.

42. Pfiffner, J. J., *et al.* Isolation of the antianemia factor (vitamin B_c in crystalline form from liver). *Science* 97:404, 1943.

43. Pfiffner, J. J., *et al.* On the peptide nature of vitamin B_c conjugate from yeast. *J. Am. Chem. Soc.* 68:1392, 1946.

44. Pfiffner, J. J., and Hogan, A. G. The newer hematopoietic factors of the vitamin B-complex. *Vitamins and Hormones* 4:1, 1946.

45. Rickes, E. L., Brink, N. G., Koniuszy, F. R., Wood, T. R., and Folkers, K. Crystalline vitamin B_{12}. *Science* 107:396, 1948.

46. Rodney, G., Swendseid, M. E., and Swanson, A. L. Tyrosine oxidation by livers from rats with a sulfasuxidine-induced pteroylglutamic acid deficiency. *J. Biol. Chem.* 168:395, 1947.

47. Ross, J. F., Belding, H., and Paegel, B. L. The development and progression of subacute combined degeneration of the spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid. *Blood* 3:68, 1948.

48. Saslaw, S., Wilson, H. E., Doan, C. A., Woolpert, O. C., and Schwab, J. L. Reactions of monkeys to experimentally induced influenza virus A infection. *J. Exper. Med.* 84:113, 1946.

48a. Shorb, M. S. Activity of vitamin B_{12} for the growth of *Lactobacillus lactis*. *Science* 107:397, 1948.

49. Smith, E. L. Purification of anti-pernicious anaemia factors from liver. *Nature* 161:638, 1948.

50. Snell, E. E., and Peterson, W. H. Growth factors for bacteria. X., Additional factors required by certain lactic acid bacteria. *J. Bact.* 39:273, 1940.

51. Spies, T. D., Vilter, C. F., Koch, M. B., and Caldwell, M. H. Observations on the antianemia properties of synthetic folic acid. *South. M. J.* 38:707, 1945.

51a. Spies, T. D., Lopez, G. G., Milanes, F., Toca, R. L., and Culver, B. Observations on the hemapoietic response of persons with tropical sprue to vitamin B_{12}. *South. M. J.* 41:523, 1948.

51b. Spies, T. D., Stone, R. E., and Aramburu, T. Observations on the antianemic properties of vitamin B_{12}. *South. M. J.* 41:522, 1948.

52. Steinkamp, R., Shukers, C. F., Totter, J. R., and Day, P. L. Urinary excretion of orally administered pteroylglutamic acid. *Proc. Soc. Exper. Biol. & Med.* 63:556, 1946.

53. Stephens, C. A. L., Jr., Borden, A. L., Holbrook, W. P., and Hill, D. F. The use of folic acid in the treatment of anemia of rheumatoid arthritis: A preliminary report. *Ann. Int. Med.* 27:420, 1947.

54. Stokstad, E. L. R., and Hutchings, B. L. The microbiological assay of *Lactobacillus casei* factor (vitamin B_c, folic acid). *Biol. Symposia* 12:339, 1947.

55. Stokstad, E. L. R., and Jukes, T. H. Absence of appreciable *L. casei* factor effect in anti-pernicious anemia liver extract. *Proc. Soc. Exper. Biol. & Med.* 62:112, 1946.

56. Stokstad, E. L. R., and Manning, P. D. V. Evidence of a new growth factor required by chicks. *J. Biol. Chem.* 125:687, 1938.

57. Stokstad, E. L. R., Regan, M., Franklin, A. L., and Jukes, T. H. Interrelationships between pteroylglutamic acid, adenine, thymine, and antagonists of pteroylglutamic acid. *Federation Proc.* 7:193, 1948.

58. SubbaRow, Y., Hastings, A. B., and Elkin, M. Chemistry of anti-pernicious anemia substance of liver. *Vitamins and Hormones* 3:238, 1945.

59. Swendseid, M. E., Bird, O. D., Brown, R. A., and Bethell, F. H. Metabolic function of pteroylglutamic acid and its hexaglutamyl conjugate. *J. Lab. & Clin. Med.* 32:23, 1947.

60. Thaysen, T. E. H. Non-tropical Sprue: A study in Idiopathic Steatorrhea. Copenhagen, Levin and Munksgaard, 1932.

61. Totter, J. R., and Sims, E. S. The influence of KCN and pteroylglutamic acid on growth and porphyrin production of *corynebacterium hoffmannii.* *Federation Proc.* 7:196, 1948.

62. Vilter, C. F., Spies, T. D., and Koch, M. B. Further studies on folic acid in the treatment of macrocytic anemia. *South. M. J.* 38:781, 1945.

63. Vilter, C. F., Vilter, R. W., and Spies, T. D. The treatment of pernicious anemia and related anemias with synthetic folic acid. *J. Lab. & Clin. Med.* 32:262, 1947.

64. Waldenström, J. Successful treatment of liver-refractory anemia with synthetic *Lactobacillus casei* factor. *Blood* 2:426, 1947.

65. Watson, J., and Castle, W. B. Nutritional macrocytic anemia, especially in pregnancy. *Am. J. M. Sc.* 211:513, 1946.

66. Watson, C. J., Sebrell, W. H., McKelvey, J. L., and Daft, F. S. Possible effectiveness of the *L. casei* factor ("folic acid") concentrates on refractory anemia and leukopenia, with particular reference to leukopenia following radiation therapy. *Am. J. M. Sc.* 210:463, 1945.

67. West, R. Activity of vitamin B_{12} in Addisonian pernicious anemia. *Science* 107:398, 1948.

68. Wills, L. Studies in pernicious anemia of pregnancy: VI., Tropical macrocytic anemia as a deficiency disease, with special reference to the vitamin B complex. *Indian J. M. Research* 21:669, 1934.

69. Wills, L., Clutterbuck, P. W., and Evans, B. D. F. A new factor in the production and cure of macrocytic anemias and its relation to other haemopoietic principles curative in pernicious anemia. *Biochem. J.* 31:2136, 1937.

70. Wills, L., and Mehta, M. M. Studies in "pernicious anemia" of pregnancy. *Indian J. M. Research* 17:777, 1930.

71. Woodruff, Calvin W., and Darby, William J. An in vivo effect of pteroylglutamic acid upon tyrosine metabolism in the scorbutic guinea pig. *J. Biol. Chem.* 172:851, 1948.

71a. Woodruff, C. W., Ripy, H. W., Peterson, J. C., and Darby, W. J. The variable response to vitamin B_{12} of megaloblastic anemia of infancy. *Pediatrics,* in press.

72. Zuelzer, W. W., and Ogden, F. N. Megaloblastic anemia in infancy. *Am. J. Dis. Child.* 71:211, 1946.

Chapter 22

CHOLINE MALNUTRITION

Charles H. Best and Colin C. Lucas

Choline was first isolated from biologic material by Strecker[146, 147] approximately one hundred years ago, but its nutritional importance has been appreciated for barely sixteen years. Interest in the possible clinical usefulness of choline stems from the fact that experimental animals fed upon diets deficient in this quaternary ammonium base or its precursors develop characteristic lesions.[17] Adult mammals—dogs, rats, and mice have been studied most extensively—subsisting on a diet low in choline develop large, fatty livers. This pathologic condition, which develops rather rapidly (three to fifteen days in the case of rats, depending upon their age, the composition of the diet, the food intake, and other factors), may be restored to normal by including adequate amounts of choline or its dietary precursors in the ration. If the deficiency persists for longer periods, animals which have extensive fatty deposits in their livers develop cirrhosis. In the early stages at least, this secondary change is also reversible if adequate choline is restored to the diet. Very young mammals (weanlings) appear to be particularly susceptible to choline deficiency during the period of most rapid growth. At this age, kidney lesions (hemorrhagic degeneration) also develop rapidly (five to fifteen days in rats) and the condition ends fatally unless an adequate amount of choline is supplied promptly. The development of these and other lesions in rats, mice, and dogs fed choline-deficient diets, and their prevention and cure by choline, have now been confirmed in many laboratories.

Recognition of the nutritional significance of choline was an outgrowth of the discovery of insulin. In one of the very early experimental studies made with commercial insulin, Bliss[23] observed that an almost completely depancreatized dog maintained with insulin for several months (June 19 to September 1, 1922), eventually died and exhibited an extremely large and fatty liver which, as we shall see, may have been due to lack of insulin or of choline. This observation, buried in a mass of other findings, did not merit any special comment at that time. Banting and Best had not observed fatty livers in their depancreatized dogs in the earliest days of insulin work because they did not conduct trials over prolonged periods. When they found that it was possible to eliminate all signs of the diabetic state from their dogs by administration of the antidiabetic hormone; that the animals could be so maintained for periods up to as long as six weeks; and that the abnormalities reappeared promptly upon cessation of the treatment, their attention became focussed on the clinical applications of insulin. It was only somewhat later, when the more extended studies of insulin-maintained depancreatized dogs were undertaken by J. J. R. Macleod and his colleagues in Toronto, that the lesions now known to be characteristic of choline deficiency were encountered.

It was noted almost simultaneously in Toronto and Chicago[2, 72] that when depancreatized dogs were maintained with insulin for periods up to seven months or even longer, the animals ultimately sickened and died. Large, yellow livers were found consistently at autopsy. The diets used would now be recognized as grossly inadequate but at that time the absence of pancreatic enzymes was believed to account in large part for the result. Some support for this hypothesis was obtained when it was found that fatty livers did not develop if raw beef pancreas was included in the diet of lean meat (500–900 Gm.) and cane sugar (100–150 Gm.) fed by Allan, Bowie, Macleod, and Robinson[2] to the depancreatized dogs. Three years later, acting upon the hypothesis that a failure in fat metabolism rather than a defect in digestion was responsible for the condition, and recalling the suggestion of Bloor[24] and of Maclean and Maclean[112] that phospholipids are concerned in fat transport, Hershey added 10 Gm. of crude egg yolk lecithin daily to the diet of 8 depancreatized dogs that had developed the typical signs of liver dysfunction (jaundice, bile pigments in the urine, and hypoglycemic reactions) on the lean-meat–sucrose rations. The animals were restored to an apparently normal condition and 2 of them, sacrificed a year later, had normal liver fat. Reporting these findings briefly from Best's laboratory in 1930, Hershey[86] concluded that pancreatic enzymes are not essential in the dog. He noted that 3 dogs had died during the year with signs suggestive of vitamin deficiency. Hershey's conclusion appeared to be supported by the report of Penau and Simmonet[127] that they were able to keep a depancreatized dog, receiving insulin but no raw pancreas (or enzymes from it) alive and well for over two years. It is significant that the diet contained large amounts of milk and bread. Hershey and Soskin[87] described in more detail the beneficial effects of feeding lecithin and noted that addition of cod liver oil and marmite, a concentrated yeast extract, to the diet greatly improved the condition of the animals without altering the essential findings.

Progress up to this point had been necessarily slow because in depancreatized dogs the typical fatty liver required from three to eleven months to develop on the diets then in vogue. Not only are the experiments with depancreatized dogs tedious, but the results are so variable that interpretation is difficult unless large numbers of animals are used. When in 1932 Best, Hershey, and Huntsman[12] found that fatty livers could be induced relatively quickly in rats, the stage was set for an accelerated elucidation of the factors involved in the production and cure of fatty livers.

On the basis of the observation that fat in the diet of depancreatized dogs aggravated the liver damage, rats were placed on high-fat, low-protein diets for thirty-five to thirty-eight days and fatty livers were obtained. In as short a period as twenty-one days liver fats averaging 18 per cent were obtained in rats consuming a diet containing 40 per cent beef dripping, 19.5 per cent each of whole cracked wheat, rolled oats, and corn meal, and 1.5 per cent bone meal. Supplements of crude egg-yolk lecithin (0.5 Gm. daily) brought the liver fat down to normal, as did crude beef-liver lecithin. That the effect was not due to some contaminant of the lecithin was shown[12] by persistence of the activity after purification of both crude products by the cadmium-chloride procedure of Levene and Rolf.[102]

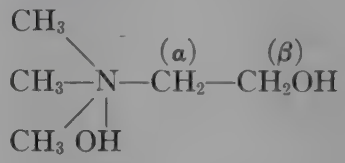
One month later the same workers[13] published a note identifying choline as the active constituent of the lecithin molecule. Two months elapsed before details of the experiments were published by Best and Huntsman,[14] who showed that neither sodium phosphate, sodium β-glycerophosphate, calcium α-glycerophosphate, sodium oleate, nor ethanolamine would reduce the liver fat to normal, but that choline did so. They published a dose-response curve, covering choline intakes from 10 to 117 mg. per rat per day, which indicated that, on the dietary regimen adopted, about 20 mg. per day exerted a maximal effect. Choline was shown to be effective subcutaneously. The similar effect of betaine on liver fat was also noted in this paper.

In 1933 Best, Ferguson, and Hershey[1[illegible]] showed that choline prevented development of fatty livers in depancreatized dogs maintained with insulin and alleviated the condition when administered in curative experiments. This effect of choline in rats and mice and in depancreatized and normal dogs has been confirmed in many laboratories. Later work indicated that other factors may contribute to the effect of the raw pancreas supplement in the diets of depancreatized dogs.

The term "lipotropic" first appeared without specific definition, in a note by Best and Ridout.[19] It was used to describe the activity of dietary factors such as choline and betaine. Three months later, Best, Huntsman, and Ridout[16] in a footnote explained that "the term 'lipotropic' is used to describe substances which decrease the rate of deposition and accelerate the rate of removal of liver fat."

CHEMISTRY

An elementary knowledge of the chemistry of choline and its precursors is essential to any discussion of choline deficiency and therapy. Although the compound was first isolated by Strecker in 1849, the name "choline" did not appear in the chemical literature until 1862.[146, 147] Its nature was finally established by Wurtz[162] who first prepared its chloride synthetically by condensing ethylene chlorhydrin with trimethylamine, thus establishing that choline is the quaternary ammonium base, trimethyl-β-hydroxy-ethylammonium hydroxide:



Choline ($C_5H_{15}NO_2$; molecular weight 121.13) is a colorless, crystalline, strongly basic substance of extraordinary hygroscopicity. The chloride, in which form it is available commercially, and, indeed, most of its salts possess similar hygroscopic properties. Unless unusual precautions are observed in storing and handling most salts of choline, they will change rapidly from the crystalline state to a sirupy condition. The free base is extremely soluble, not only in water, but also in methyl and ethyl alcohols. It is less soluble in the higher alcohols. It is only slightly soluble in dry amyl alcohol, dry acetone, and chloroform, and is insoluble in pure, dry ether, petroleum ether, and benzene.

All salts of choline prepared to date are very soluble in water except the periodide, reineckate, phosphotungstate, phosphomolybdate, and the double salts with gold chloride, mercuric chloride, potassium mercuric iodide (Mayer's reagent), and potassium bismuth iodide (Dragendorff's or Kraut's reagent). These have all been used in the isolation of choline from natural products, and the first two have been the basis for the most commonly used microchemical methods for determining choline.

The careful quantitative studies of Staněk,[144] Sharpe,[138] and Roman,[132] led to the excellent periodide micromethod of Erickson, Avrin, Teague, and Williams.[122]

The use of ammonium reineckate as a reagent for the microdetermination of choline has been studied in many laboratories.[7, 67, 85, 92, 122, 139, 145, 159] As the experimental conditions have been more rigorously controlled, the errors (some positive, some negative) have been minimized. The reineckate procedure of Glick[76] is not difficult to perform and gives reproducible results within the range 0.2 to 5 mg. Marenzi and Cardini[114] have described a more sensitive modification of the reineckate procedure, in which the chromium of the choline reineckate precipitate is oxidized with alkaline hydrogen peroxide and the resulting chromate is determined colorimetrically with diphenyl-carbazide.

Other micromethods, depending upon simple alkaline degradation[99] or oxidative degradation[105] of choline to the volatile base trimethylamine, have been described.

None of the quantitative methods are specific for choline. The most specific and sensitive procedure for detecting choline and estimating small amounts is bioassay after acetylation, but this procedure is beset with certain hazards.[43, 74] Equally specific and sensitive, and easier to perform, is the microbiologic assay[89] utilizing the *cholineless* mutant (No. 34486), produced by ultraviolet radiation of the wild form, of the bread mould *Neurospora crassa*. The interference encountered in this procedure from naturally occurring and synthetic substances allied to choline has been studied by Horowitz, Bonner, and Houlahan.[90] Handler[84] has recently given details of several of these methods for the determination of choline in biologic materials.

Unfortunately, no specific precipitant or color test for choline is known. These somewhat extended remarks on the detection and estimation of choline are included to serve as a warning that some of the data on the occurrence (or absence) of choline in foods, tissues, or tissue extracts may be seriously in error. The methods are based upon the properties of *free* choline, from which desired derivatives are made under standard conditions. Since in most tissues the amount of choline present in the free form is 1 per cent or less of the total present, failure to do a proper extraction and complete hydrolysis will give grossly erroneous analytical results. (For further discussion see Best[17] and others.[76, 80, 84, 145])

SOURCES

Data on the distribution of choline are scattered and often of questionable reliability. Guggenheim[80] gives over one hundred references from the older literature concerning the occurrence of choline in many plants and in various animal tissues. Some of the more modern determinations are given in Table 31.

TABLE 31. TOTAL CHOLINE CONTENT OF RAT TISSUES[74]

ADULT WHITE RATS (WISTAR STRAIN); AVERAGE WEIGHT 200 GM.; STARVED TWENTY-FOUR HOURS BEFORE USE.

Tissue	*Total no. of rats*	*Average choline content mg. 1100 Gm.*
Spermatic fluid	5	514
Spinal cord	2	370
Brain	10	325
Adrenals	15	304
Cerebellum	5	296
Cerebral hemispheres	4	274
Liver	28	260
Pancreas	14	232
Pituitary	8	224
Kidneys	9	202
Thyroid	11	167
Lungs	5	164
Heart	8	158
Lymph glands	3	152
Stomach	4	152
Spleen	7	151
Small intestine	6	142
Large intestine	3	139
Salivary glands	2	131
Tongue	6	123
Thymus	3	113
Skeletal muscle	9	100
Uterus	5	74
Skin	2	64
Bone	4	44
Connective tissue	1	40
Fat	6	23
Blood		
starved	4	22
fed	1	31

No difference was detected between the choline contents of tissues from male and female animals.

The total choline content of a number of common foodstuffs has been determined.[34, 68, 74, 111, 129] Egg yolk, by far the richest natural source, contains up to 1750 mg. per 100 Gm.,[34] liver contains from 300 to 700 mg., brain 200 to 400, kidney 100 to 300 and heart about 200 mg. per 100 Gm.[34, 68, 111] Lean meats contain from 40 to 120 (usually about 60 to 80) mg. per 100 Gm. and wheat flour (white) has been found to contain from 25 to 140 mg.[34, 74] Dried bakers' and brewers' yeast contain from 240 to 360 mg. per 100 Gm.[34, 74] Soya bean meal is also an excellent source of choline (280 to 350 mg. per 100 Gm.);[68, 129] peanut meal (230 to 250 mg.) and wheat germ (400 mg.) are other rich sources. Fruit juices and vegetables are, in general, very poor sources of choline.[34] Edible oils and fats are practically free from choline.[34, 74]

Free choline is rarely encountered in plants or in the tissues or excretions of animals in more than trace amounts. Choline occurs in nature mainly as complex phosphoric esters—the phospholipids (lecithin, sphingomyelin, and possibly similar complexes not yet identified). Since the phospholipids are found in all living cells, they are believed to be essential protoplasmic components. The ubiquity of choline in foodstuffs and tissues is, therefore, not surprising. Other esters of choline have been encountered in natural products, usually in very small quantity.[56, 71]

Values which we have obtained by actual analysis in Toronto[101] for the daily choline intake of adults on average mixed diets (250 to 600 mg.) agree with calculated values (300 to 500 mg.) reported by Borglin[34] from Sweden. Johnson, Hamilton, and Mitchell[93] determined the daily choline intakes of young men in the United States. Unfortunately, it is not clear whether the values reported are daily averages or the total for the five-day test period.

Large doses of choline chloride fed to sheep and dogs failed to increase the levels of either free or total choline in plasma, liver, or kidney; only a very small portion (0.5 to 2.5 per cent) was recovered in the twenty-four-hour urine).[107] Human subjects excreted equally small proportions (0.7 to 1.5 per cent) of the choline intake.[93]

DIETARY PRECURSORS OF CHOLINE

That other substances, both natural and synthetic, possess lipotropic activity soon became apparent. Best and Huntsman[14] had noted the lipotropic activity of betaine, and the same workers in 1935[15] observed that addition of purified casein (20 per cent) to a basal diet of pure sucrose which had occasioned an increase of liver fat, prevented the rise.

Channon and Wilkinson[48] showed that with amounts of casein in the diet increasing up to 50 per cent, there is a progressive decrease in liver fat. Best, Grant, and Ridout[11] confirmed these results and reported that dried egg white and alcohol-extracted beef muscle also exhibit lipotropic properties but that gelatin does not. The lipotropic activity of a number of proteins was studied in Channon's laboratory[44] and marked differences were noted.

Channon and his colleagues embarked on a systematic study of the amino acids to see whether any possessed lipotropic properties. They noted[9] that cystine supplements to the basal diet had the opposite effect, confirming an earlier observation of Curtis and Newburgh.[54] In 1937, while Channon's group were continuing their study of the other amino acids, Tucker and Eckstein[149] made the important discovery that methionine possesses marked lipotropic activity.

Attempts to determine whether or not the opposing influences of the methionine and cystine contents of proteins would account for their lipotropic characteristics, as suggested by Tucker and Eckstein, were strangely unsuccessful. In the first place, the so-called *toxic effects* of small cystine supplements,[53, 54, 78, 79, 103, 121, 149] proved undemonstrable when gliadin[150] or egg albumin[45] was used in place of casein in the basal diet. Moreover, Mulford and Griffith[120] showed later that if 30 per cent (instead of 5 per cent) casein is used in the basal diet, toxic effects of the cystine supplements are not demonstrable. Addis, MacKay, and MacKay[1] had earlier noted that cystine supplements to moderately high protein diets were not harmful. Since cystine is not always toxic or antilipotropic, other dietary factors are obviously involved; simultaneous deficiencies of lipotropic factors and amino acid sulphur must exist in the basal ration in order to obtain the "toxic" effect of small supplements of cystine. These toxic effects are actually due to a deficiency of choline or of dietary labile methyl groups, which are necessary for the in vivo synthesis of choline. The condition is cured or prevented by adding choline or methionine to the ration.[106, 120] Best and Ridout[20] noted that the d- and l-forms of methionine possessed essentially similar lipotropic activity, and they concluded that factors other than the methionine and cystine content of a protein are involved in explaining its lipotropic effect. Channon, *et al.*[46] came to the same conclusion, but this view was not shared by the workers at Ann Arbor.[151] The importance of the nutritional adequacy of the diet, especially with respect to essential amino acids, was pointed out by Beveridge, Lucas, and O'Grady,[21] who later[22] thus accounted for some of the discrepancies in the literature on this phase of the subject.

TRANSMETHYLATION

The nature of some of the biochemical relationships between choline, methionine, and other substances possessing lipotropic activity, has been elucidated by the use of labeled molecules, especially those containing either "heavy" or radioactive isotopes. Methionine has been shown to possess a "labile" methyl group[63] which can methylate aminoethanol to form choline. In those species in which this transmethylation process occurs, methionine can act as a precursor (i.e., dietary substitute) for choline. While the methyl group of choline is also labile,[140] choline cannot entirely replace methionine in the diet. Methionine has a dual nutritional role: (1) as a source of organic sulphur for two important building stones of tissue—it may be used either as methionine per se or as a precursor of cystine;[148] (2) as a source of labile methyl groups for the formation of choline and for the production of other methylated compounds involved in the metabolic cycle. Choline and methionine supplements are thus maximally interchangeable in a diet only when the deficiency to be made good is one involving choline or labile methyl groups exclusively, i.e., the basal minimum of dietary methionine must be supplied and organic sulphur in the basal diet must be adequate. Choline can replace methionine completely in a diet only under experimental conditions, when the amino acid homocysteine (or homocystine) is present in adequate amounts. This synthetic amino acid, which is not known to occur in foods, is converted to methionine by a labile methyl group released from the choline. Indeed, this is the conversion that occurred in the experiments of Rose and Rice[133] and which might easily have been interpreted as evidence for the nonessentiality of methionine, or at least for its replaceability by homocystine, had not du Vigneaud, Chandler, Moyer, and Keppel[64] reported simultaneously that rats not only fail to grow on a synthetic diet containing homocysteine (or homocystine) in place of methionine, but that they lose weight and die with fatty livers unless choline is added, in which case growth is promptly resumed. Attempts to explain the apparently contradictory results led to the discovery of transmethylation. An account of the earlier work in this field has been given by du Vigneaud[61, 62] and more recent developments have been reviewed by Jukes.[95]

Methionine and cystine supplements are maximally interchangeable only when the deficiency in the basal diet concerns exclusively the organic sulphur requirement over and above the methionine minimum, i.e., choline or labile methyl groups and "essential methionine" must be adequate in the basal diet. Some of the evidence in support of these statements has been presented by Jukes[95]; data obtained in our laboratory offer further support.[106]

There is some evidence that only one of the three methyl groups of choline, or of betaine, is labile.[65, 66] The resulting products (dimethylaminoethanol or dimethylglycine, respectively) do not promote the growth of young rats on a "methyl-free" purified diet containing homocystine, as do the parent compounds. Indeed, dimethylaminoethanol acts as a methyl acceptor rather than as a donor.

Only five compounds (lecithin, choline, betaine, dimethyl-ethyl-hydroxyethyl ammonium chloride, and the calcium salt of choline-phosphoric acid) have been found to possess labile methyl groups, as measured by the ability to support growth when added to a methionine-free, choline-free basal diet containing homocystine.[38] Methionine is, of course, a sixth compound in this class. Arsenocholine and the tri-ethyl homologue of choline do not possess labile methyl groups, yet both exhibit lipotropic activity[47, 155] and protect against kidney hemorrhage in weanling rats.[100, 156] This suggests that removal of liver fat and protection of the rapidly developing kidney are not due to labile methyl groups, but to choline per se, or to analogous or homologous compounds so similar in molecular structure as to replace choline in the tissue complexes. That both of these unnatural substances, when fed, do actually replace choline in the "lecithin" of liver lipids, has been proved.[109, 110, 157]

MODE OF ACTION OF CHOLINE

These observations suggest that choline exerts its lipotropic effect as an intact molecule and that incorporation into liver phospholipid may be an essential step in the process. Strong support for this view seemed to be forthcoming when Chaikoff and others reported in a series of papers the accelerated turnover of liver phospholipid-P when choline was injected or ingested.[37] It was assumed that other constituent parts of the molecule were undergoing similar accelerated turnover, thus explaining the increased rate of removal of liver fat. Methionine also caused an accelerated turnover of liver phospholipids. An awkward discrepancy resulted from the finding that cystine and cysteine, although *not lipotropic*, also caused an increase in the specific activity of liver phospholipids.

A recent communication in *Nature*[128] reveals that eight years ago data were obtained in the Biochemistry Department of the University of Liverpool which are even more disturbing to the generally accepted hypothesis concerning the mode of action of lipotropic agents. The war, and later the death of one of the experimenters, delayed publication of the fact that ethanolamine, which is not lipotropic, also increases the turnover rate of liver phospholipids. This effect is principally on the ethanolamine-containing cephalin fraction, but the choline-containing phospholipid is also affected. Indeed, at equimolar dosage ethanolamine is more active in stimulating phospholipid-P turnover than is choline. It is obvious that an extensive modification of the older hypothesis or the formulation of a new one, to explain the action of choline, will be necessary.

CHOLINE REQUIREMENT

It has been indicated above that factors other than the supply of choline and labile methyl groups are concerned in the lipotropic effects of any given diet. The species and strain and also the age of the animal, its rate of growth, the nutritional adequacy of the diet with respect to calories, minerals, vitamins, and essential amino acids, are all important. There are indications that environmental temperature, activity, and other, as yet unrecognized, factors may alter the degree of response in a group of animals on test diets. In general, the better the diet fed to a growing animal, the more rapid the growth and the greater the requirement for lipotropic factors. The full-grown animal requires less methionine for maintenance, hence can use more of a constant dietary supply for lipotropic action and therefore requires less dietary choline than does the rapidly growing young one. Discussion of the influence of individual vitamins would be lengthy and would add but little to our understanding of the lipotropic requirements, particularly since most of the test diets used to date have possessed multiple dietary deficiencies. These findings may be summarized by the statement that when appetite and food intake are increased by adding vitamins to inadequate diets the choline requirement is augmented.[18, 83] The total choline requirement, even of rats, is not readily determined. The amount of choline needed in the diet depends, of course, on the methionine and betaine content of the ration.

Best, Hershey, and Huntsman[12] pointed out in 1932 that there is a marked difference in the choline requirements of different strains of rats. Copeland[52] has shown that weanlings of a Wisconsin hooded strain of rats require about twice as much choline per day to protect against hemorrhagic kidneys as do those of the Wistar strain (10 mg. as against 4-6 mg.) on the same hypolipotropic diet. Welch and Welch[158] have published a dose-response curve for mice on a low-protein, high-fat diet, which indicates a requirement of about 10 mg. per 2 Gm. of low-protein, high-fat diet to maintain a normal level of liver lipids in that species.

Entenman and Chaikoff[69] estimate the choline requirement of the depancreatized dog at about 35 mg. per Kg. body weight per day.

EXPERIMENTAL CIRRHOSIS

In 1938 Chaikoff, Connor, and Biskind[39] observed that cirrhosis develops in depancreatized dogs maintained for long periods with insulin. Connor and Chaikoff[50] produced cirrhosis in normal dogs by feeding a high fat diet with alcohol, and in 1940 Chaikoff and Connor[38] showed that normal dogs on a high-fat diet without alcohol developed cirrhosis (see also Chaikoff *et al*[40]). Further evidence that diet, rather than alcohol or other toxic agents, was probably in many cases the primary etiologic factor in the production of the condition was indicated by the findings of Blumberg[26] and his colleagues[27, 29] that rats on high-fat, low-protein diets develop cirrhosis which the investigators later showed could be prevented by including choline[28, 30] or methionine[25] in the diet.

Meanwhile, in 1939, György and Goldblatt[81] had reported observing, during a two-year period, unexplained deaths in rats on experimental diets designed to be deficient in pyridoxine. The animals did not exhibit specific signs of the deficiency intended nor did they die from intercurrent infections. Yellowish red patches noticed on a liver eventually drew attention to this organ. Fatty degeneration, focal and massive necrosis, and in some cases fibrosis, were often observed. Addition of yeast or yeast extract prevented the hepatic injury. Later these workers showed[82] that the lesions developed more regularly if the protein (casein) content of the diet was reduced from 18 per cent to 10 per cent. Daily addition of 10 to 50 mg. of cystine accentuated the cirrhosis. Daily addition of yeast or of 10 to 20 mg. of choline reduced the incidence and severity of the liver injury.

Almost simultaneously, in 1940 Rich and Hamilton[130] and Spellberg and Keeton[142] showed that cirrhosis could be produced by dietary means in rabbits and guinea pigs, respectively, and that the effect is prevented by including yeast in the diet. Although Spellberg, Keeton, and Ginsberg[143] did not believe choline to be a factor, a preventive effect of choline in rabbits as well as in rats was found by Blumberg, Mackenzie, and Seligson[31] under different experimental conditions. Fouts[75] observed a beneficial effect of choline and casein supplements in diets which otherwise produced cirrhosis in dogs.

In 1941, Lillie, Daft, and Sebrell[104] produced cirrhosis in rats by a low protein diet (4 per cent casein). The condition was aggravated by substituting 20 per cent alcohol for the drinking water. The addition of 0.5 per cent cystine to a diet containing 4 per cent casein and 5 per cent fat gave consistent and fairly rapid production of cirrhosis in rats drinking 20 per cent alcohol.[55] Supplements of choline chloride (20 mg. daily), methionine (to 0.7 per cent in the diet) or casein (to 30 per cent in the diet) prevented the cirrhosis. Subsequent papers from this group and from other laboratories have shown that, while the presence of alcohol is not necessary to produce liver lesions, its presence tends to aggravate the cirrhosis caused by inadequate diets.

Webster[153, 154] fed a low-protein (8 per cent casein), high-fat (40 per cent) diet to produce cirrhosis in rats; betaine hydrochloride (50 mg. daily) diminished the severity of the lesion, cystine and cholesterol supplements aggravated the condition. Brewers' yeast, molasses, or increased dietary protein (to 25 per cent) prevented the hepatic and renal lesions produced by the basal ration.

Cirrhosis caused by exposure to noxious chemicals has also been studied experimentally. The protective and curative properties of adequate diets are well established. The key positions of choline, methionine (a dietary precursor of choline), and protein (the normal dietary source of methionine) in the recovery phase are becoming generally recognized.[95, 137]

From the point of view of the experimentalist, the present knowledge of the etiology and treatment of dietary cirrhosis in animals would justify the following recommendations for clinical trial: (1) The provision of adequate amounts of choline or of its dietary precursors; (2) The provision of adequate caloric intake; (3) The provision of all the essential amino acids, the minerals, the recognized vitamins, and other accessory food factors; (4) The avoidance of excess fat and cholesterol in the diet. Each of these points may be discussed very briefly in the light of the findings presented earlier.

1. The amount of choline required obviously will depend on the amount of dietary methionine or betaine which is available for lipotropic purposes. The demand for methionine for other than lipotropic purposes is increased during growth and when the cystine content of the diet is low. A normal diet provides daily from 200 to 800 mg. of choline and from 2 to 4 Gm. of methionine.

It should be emphasized again that average diets containing a normal amount of choline and its precursors, methionine or betaine, should provide an adequate amount of the lipotropic agents. If satisfactory amounts of these substances are provided from the normal diet, no demonstrable effect would be expected from the addition of further amounts. If, however, as has been emphasized elsewhere, there should be interference with protein digestion, the work of Chaikoff and his colleagues[41, 42] suggests that inadequate amounts of methionine may be liberated and that this will result in a lack of available choline. Under these circumstances methionine and choline supplements may be necessary. An adequate supply for this purpose should be 2 to 4 Gm. of choline daily, as chloride or citrate. If methionine, an expensive dietary precursor of choline, is used, 6 to 9 Gm. might be provided.

Choline or methionine should be administered by mouth unless there is evidence that they will not be absorbed from the intestine. Choline has the same properties as its more potent acetyl derivative, the neurohumor acetylcholine. Choline given intravenously or subcutaneously in large doses may cause a profound fall in blood pressure, slowing of the heart, stimulation of intestinal movements, and other parasympathetic effects. These are not "side effects" but the well-recognized pharmacologic actions of the compound. The toxicity of choline depends on the rate and route of administration. When given very rapidly into a vein, 35 to 65 mg. of choline chloride per Kg. may be lethal to a cat. If administered slowly to the same species (0.8 mg. per Kg. per minute) as much as 200 mg. per Kg. may be injected intravenously without harmful effects.[4] Since such a common human food as egg yolk contains over 1700 mg. of choline per 100 Gm., it is a matter of common experience that large amounts may be ingested in a combined form without ill effects. Choline or methionine as normal constituents of our diet are presumably liberated slowly in the intestine and absorbed gradually with the other food constituents. An effort to simulate this procedure should be made when they are used therapeutically as lipotropic agents. Divided doses given with or immediately after meals should be prescribed. As stated above, 2 to 4 Gm. in capsules or in solution, given in divided doses, would appear to be the maximum dosage of choline necessary, but some clinicians are prescribing up to 25 Gm. per day.

2. Provision of an adequate caloric intake is important in the treatment of a condition where restoration of tissues is an objective. To avoid feeding large amounts of fat in the treatment of cirrhosis, carbohydrate should be used to provide the calories necessary. The carbohydrate will exert a sparing action on the protein requirement and will also provide material for glycogen synthesis in the liver. There is considerable experimental and clinical evidence to indicate that conditions which encourage glycogen synthesis in the liver are favorable for the protection of that tissue against damage and for its recovery from injury.[3, 32, 33, 60, 94, 134, 160]

3. It is obvious that all of the essential amino acids should be present in the diet in adequate amounts if regeneration of tissue is to be facilitated. Minerals and accessory food factors are also required and the latter exert the additional action of stimulating the appetite and thus augmenting the intake of all the other essentials.

4. Since the experimental evidence demonstrates the injurious effects of excess dietary fat and cholesterol on liver tissue, it is probably wise to keep these constituents well within normal limits in the diets of patients with cirrhosis.

CLINICAL EXPERIENCES

The clinical studies of Patěk and his collaborators[123-126] are justly credited with focusing the attention of clinicians on the favorable results of the dietary treatment of Laennec's cirrhosis. A significant number of patients with severe liver failure and a larger percentage of those with moderate liver damage have been successfully treated by dietary means. Fleming and Snell[73] reported that increasing the protein content of the ration from a low level to 110 Gm. per day improved the results in their study of the dietary treatment of cirrhosis.

Broun and Muether[35] reported that 4 patients with cirrhosis treated with choline chloride (1 Gm. per day) for several years showed improvement. No data are available, however, for a comparable group of patients on an identical diet without added choline. Russakoff and Blumberg[135] gave choline chloride in doses from 1.5 to 6 Gm. per day to patients with decompensated portal cirrhosis maintained on diets low in fat and high in carbohydrate and protein. The results suggested that the choline supplement produced improvement beyond that occasioned by the dietary regimen adopted. This paper provides an accurate review of previous work. In 1945 Goldstein and Rosahn[77] reported on 4 patients with cirrhosis treated by choline, alone or combined with inositol. All 4 showed clinical improvement, but this might have been due entirely to the high-carbohydrate, high-protein, low-fat diet used. Beams[6] described beneficial effects of choline chloride (1.5 to 3 Gm. daily) in patients with cirrhosis when ascites and large palpable livers were noted, but no such favorable response was secured in 12 cases of cirrhosis where the livers were not enlarged. Twenty-three patients with large livers were studied, 8 received the choline chloride plus an equal amount of cystine, for one to five months. The remaining fifteen were maintained on the basal diet (high-protein, low-fat, with 30 to 45 Gm. of brewers' yeast daily). Eight deaths occurred in one year in the control group, only 1 in the treated group. Man, Kartin, Durlacher, and Peters[113] reported that in 3 patients no demonstrable effect on cirrhosis was observed when 10 to 25 Gm. of choline chloride was given daily. Morrison[117, 118] has applied all the principles which the experimentalist would recommend and reports favorable results.

Although Beattie and Marshall[8] claimed that patients with infectious hepatitis were greatly benefited by 10-Gm. doses of methionine given intravenously, subsequent workers have failed to confirm this conclusion. Doses of choline chloride varying from 1.5 Gm. daily[131] through 5 Gm.[88] to 20 Gm.[5] have not been found to exert any demonstrable effect in infectious hepatitis.

Because of some unconfirmed reports that choline produces anemia in dogs,[49, 57, 58] it is of interest to record that the chloride in doses of 10 mg. per Kg. of body weight, taken orally three times daily for ninety days by three men, failed to produce either anemia or macrocytosis.[30] Watson and Castle[152] gave choline chloride (17 mg. per Kg.) for seventy days, without other medication, to a patient with cirrhosis of the liver and macrocytic anemia; his red cell count and hemoglobin increased steadily. Moosnick, Schleicher, and Peterson[116] gave choline chloride intravenously (1 Gm. daily) to a patient with pernicious anemia who showed fatty metamorphosis of the liver and bone marrow. The patient, who had failed to respond to liver extract, showed prompt improvement, i.e., a reticulocyte peak of 6 per cent in three days, with steady increases in both hemoglobin and red cell count. They suggest that the anti-pernicious-anemia factor was ineffective because the liver was fatty. Davis and Brown[59] present evidence that in certain cases of megaloblastic anemia choline is effective in overcoming, partially or completely, a refractoriness to parenteral liver therapy.

Evidence is accumulating that some types of clinical cirrhosis are favorably affected by dietary treatment. While the clinician will naturally wish to provide all of the factors which may exert beneficial effects, a very great deal would be learned if it were possible to test the lipotropic agents individually and to study an equal number of control cases receiving exactly the same diet without the supplement of the lipotropic factors. All the experimental evidence indicates that choline and its precursors are needed for the recovery of liver tissue after injury. The clinician should appreciate that the normal diet usually provides adequate amounts of these factors to permit recovery of hepatic tissue. Under experimental conditions, when the lipotropic agents are absent from the diet the liver does not recover from dietary cirrhosis, carbon tetrachloride cirrhosis, or the toxic effects of phosphorus.

It is to be hoped that well-controlled clinical investigations of the therapeutic role of the lipotropic agents will be made in countries where there is a high incidence of cirrhosis which is thought to be of dietary origin.

ADDENDUM

Some interesting recent developments since the first draft of this chapter was written should be recorded here. Maw and du Vigneaud (*J. Biol. Chem.* 176, 1029, 1948) have recently prepared the sulfur analogue of choline (dimethyl-β-hydroxyethyl sulfonium chloride). It does not support growth when added to diets containing homocystine but devoid of choline and methionine (so-called methyl-free diets), i.e., it does *not* contain labile methyl groups. It does prevent fatty livers, however, and protects weanling rats from developing renal lesions. It is a third example of a synthetic compound possessing lipotropic activity but lacking a labile methyl group; like the other two (arsenocholine and "tri-ethyl" choline) when fed it is incorporated as an intact molecule into liver lecithin. The absence of lability of the methyl groups was surprising since dimethyl-thetin, the sulfur analogue of betaine, does possess labile methyl groups (*J. Biol. Chem.* 174:477, 1948). Recent investigations of Dubnoff (*Federation Proc.* 8:455, 1949) indicate that the methyl group of choline is labile only in those species which possess choline oxidase; this may mean that choline *per se* does not possess a labile methyl group but that it is only after conversion to betaine that lability is conferred on the methyl groups.

BIBLIOGRAPHY

1. Addis, T., MacKay, E. M., and MacKay, L. L. The effect on the kidney of the long continued administration of diets containing an excess of certain food elements. 1. Excess of protein and cystine. *J. Biol. Chem.* 71:139, 1926–27.
2. Allan, F. N., Bowie, D. J., Macleod, J. J. R., and Robinson, W. L. Behaviour of depancreatized dogs kept alive with insulin. *Brit. J. Exper. Path.* 5:75, 1924.
3. Althausen, T. L. Dextrose therapy in diseases of the liver. *J.A.M.A.* 100:1163, 1933.
4. Arai, K. Choline and the hormone of intestinal motion: VI, Experimental therapy of gastrointestinal paralysis after peritonitis and laparotomy. *Arch. f. d. ges. Physiol.* 193:359, 1922.
5. Barclay, J. A., Kenny, R. G., and Cooke, W. T. Treatment of infective hepatitis. *Brit. M. J.* 2:298, 1945.
6. Beams, A. J. Treatment of cirrhosis of the liver with choline and cystine. *J.A.M.A.* 130:190, 1946.
7. Beattie, F. J. R. A colorimetric method for the determination of choline and acetylcholine in small amounts. *Biochem. J.* 30:1554, 1936.
8. Beattie, J., and Marshall, J. The sulphur-containing amino acids in jaundice. *Nature* 154:547, 1944.
9. Beeston, A. W., and Channon, H. J. Cystine and the dietary production of fatty livers. *Biochem. J.* 30:280, 1936.
10. Best, C. H., Ferguson, G. C., and Hershey, J. M. Choline and liver fat in diabetic dogs. *J. Physiol.* 79:94, 1933.
11. Best, C. H., Grant, R., and Ridout, J. H. The "lipotropic" effect of dietary protein. *J. Physiol.* 86:337, 1936.
12. Best, C. H., Hershey, J. M., and Huntsman, M. E. The effect of lecithine on fat deposition in the liver of the normal rat. *J. Physiol.* 75:56, 1932.
13. Best, C. H., Hershey, J. M., and Huntsman, M. E. The control of the deposition of liver fat. *Am. J. Physiol.* 101:7P, 1932.
14. Best, C. H., and Huntsman, M. E. The effects of the components of lecithine upon deposition of fat in the liver. *J. Physiol.* 75:405, 1932.
15. Best, C. H., and Huntsman, M. E. The effect of choline on the liver fat of rats in various states of nutrition. *J. Physiol.* 83:255, 1935.
16. Best, C. H., Huntsman, M. E., and Ridout, J. H. The "lipotropic" effect of protein. *Nature* 135, 821, 1935.

17. Best, C. H., and Lucas, C. C. Choline: Chemistry and significance as a dietary factor. *Vitamins and Hormones* 1:1, 1943.
18. Best, C. H., Lucas, C. C., and Ridout, J. H. Unpublished data.
19. Best, C. H., and Ridout, J. H. Choline and the fatty liver produced by feeding cholesterol. *J. Physiol.* 84:7P, 1935.
20. Best, C. H., and Ridout, J. H. The lipotropic action of methionine. *J. Physiol.* 97:489, 1940.
21. Beveridge, J. M. R., Lucas, C. C., and O'Grady, M. K. The effect of the nature and level of protein and amino acid intake upon the accumulation of fat in the liver. *J. Biol. Chem.* 154:9, 1944.
22. Beveridge, J. M. R., Lucas, C. C., and O'Grady, M. K. The effect of dietary proteins and amino acids on liver fat. *J. Biol. Chem.* 160:505, 1945.
23. Bliss, S. W. Effects of insulin on diabetic dogs. *J. Metab. Research* 2:385, 1922.
24. Bloor, W. R. Biochemistry of the fats. *Chem. rev.* 2:243, 1925.
25. Blumberg, H. Unpublished data (quoted from Rossakoff and Blumberg[135]).
26. Blumberg, H. Attempts to produce tumors in rats by feeding crude wheat germ oil made by prolonged ether extraction. *Pub. Health Rep.* 55:531, 1940.
27. Blumberg, H., and Grady, H. G. The production of diffuse nodular cirrhosis of the liver in rats on high-fat, low-protein diets. *J. Biol. Chem.* 140:15, 1941.
28. Blumberg, H., and Grady, H. G. The production of diffuse nodular cirrhosis of the liver in rats on high fat-low protein diets. Presented before Am. Soc. Exper. Path., Chicago, April 19, 1941.
29. Blumberg, H., and Grady, H. G. Production of cirrhosis of the liver in rats by feeding low protein, high fat diets. *Arch. Path.* 34.1035, 1942.
30. Blumberg, H., and McCollum, E. V. Prevention by choline of liver cirrhosis in rats on high-fat, low-protein diets. *Science* 93:598, 1941.
31. Blumberg, H., and MacKenzie, C. G., and Seligson, D. The prevention by choline, methionine or casein of dietary cirrhosis of the liver in rats and rabbits. *Federation Proc.* 1:187, 1942.
32. Bollman, J. L. The influence of diet on the resistance to experimental hepatitis. *S. Clin. North America* 23:1102, 1943.
33. Bollman, J. L., and Mann, F. C. Physiology of the impaired liver. *Ergebn. Physiol.* 38:445, 1936.
34. Borglin, N. E. On the excretion of choline in urine. *Acta pharmacol. et toxicol.* 3, suppl. 1, 1947.
35. Broun, G. O., and Muether, R. O. Treatment of hepatic cirrhosis with choline chloride and diet low in fat and cholesterol. *J.A.M.A.* 118:1403, 1942.
36. Cartwright, G. E., and Wintrobe, M. M. Effect of administration of choline chloride on hematologic picture in human beings. *J.A.M.A.* 127:911, 1945.

37. Chaikoff, I. L. The application of labeling agents to the study of phospholipid metabolism. *Physiol. Rev.* 22:291, 1942.

38. Chaikoff, I. L., and Connor, C. L. Production of cirrhosis of the liver of the normal dog by high fat diets. *Proc. Soc. Exp. Biol. & Med.* 43:638, 1940.

39. Chaikoff, I. L., Connor, C. L., and Biskind, G. R. Fatty infiltration and cirrhosis of liver in depancreatized dogs maintained with insulin. *Am. J. Path.* 14:101, 1938.

40. Chaikoff, I. L., Eichorn, K. B., Connor, C. L., and Entenman, C. The production of cirrhosis in the liver of the normal dog by prolonged feeding of a high fat diet. *Am. J. Path.* 19:9, 1943.

41. Chaikoff, I. L., Entenman, C., and Montgomery, M. L. Free methionine prevents fatty livers in completely depancreatized dogs maintained with insulin and fed a lean meat diet. *J. Biol. Chem.* 160:489, 1945.

42. Chaikoff, I. L., Entenman, C., and Montgomery, M. L. A comparison of hydrolyzed and unhydrolyzed casein in the prevention of fatty livers of the completely depancreatized dog maintained with insulin. *J. Biol. Chem.* 168:177, 1947.

43. Chang, H. C., and Gaddum, J. H. Choline esters in tissue extracts. *J. Physiol.* 79:255, 1933.

44. Channon, H. J., Loach, J. V., Loizides, P. A., Manifold, M. C., and Soliman, G. The effects of protein in the prevention of dietary fatty livers. *Biochem. J.* 32:976, 1938.

45. Channon, H. J., Manifold, M. C., and Platt, A. P. The action of sulfur-containing amino acids and proteins on liver-fat deposition. *Biochem. J.* 34:866, 1940.

46. Channon, H. J., Mills, G. T., and Platt, A. P. The action of amino acids and proteins on liver fat deposition. *Biochem. J.* 37:483, 1943.

47. Channon, H. J., and Smith, J. A. B. The dietary prevention of fatty livers. Triethyl-β-hydroxyethyl-ammonium hydroxide. *Biochem. J.* 30:115, 1936.

48. Channon, H. J., and Wilkinson, H. Protein and the dietary production of fatty livers. *Biochem. J.* 29:350, 1935.

49. Clarkson, M. F., and Best, C. H. Absence of a macrocytic anemia in dogs fed choline or choline plus fat. *Science* 105:623, 1947.

50. Connor, C. L., and Chaikoff, I. L. Production of cirrhosis in fatty livers with alcohol. *Proc. Soc. Exper. Biol. & Med.* 39:356, 1938.

51. Contardi, A., and Ercoli, A. The enzymic splitting of lecithins and lysocithins. *Arch. di sc. biol.* 21:1, 1935.

52. Copeland, D. H. Strain differences in the choline requirement of rats. *Proc. Soc. Exper. Biol. & Med.* 57:33, 1944.

53. Cox, G. J., Smythe, C. V., and Fishback, C. F. The nephropathogenic action of cystine. *J. Biol. Chem.* 82:95, 1929.

54. Curtis, A. C., and Newburgh, L. H. The nephrotoxic action of ingested cystine. *J. Clin. Investigation* 2:611, 1926.

55. Daft, F. S., Sebrell, W. H., and Lillie, R. D. Production and prevention of dietary liver cirrhosis. *Proc. Soc. Exper. Biol. & Med.* 48: 228, 1941.
56. Dale, H. H. The occurrence in ergot and action of acetylcholine. *J. Physiol.* 48, iii, 1914.
57. Davis, J. E. Depression of the normal erythrocyte number by soybean lecithin or choline. *Am. J. Physiol.*, 142:65, 1944; also pp. 213 and 402.
58. Davis, J. E. Hyperchromic anemia produced by choline or acetylcholine and the induced remission of both by folic acid or liver injection. The probable mechanism of action of liver and folic acid in treatment of anemia. *Am. J. Physiol.* 147:404, 1946.
59. Davis, L. J., and Brown, A. The erythropoietic activity of choline chloride in megaloblastic anemias. *Blood,* 2:407, 1947.
60. Davis, N. C. and Whipple, G. H. Liver injury in chloroform anaesthesia. *Arch. Int. Med.* 23:612, 1919.
61. Du Vigneaud, V. Interrelationships between choline and other methylated compounds. *Biol. Symposia,* 5:234, 1941.
62. Du Vigneaud, V. The significance of labile methyl groups in the diet and their relation to transmethylation. *Harvey Lect.,* 38:39, 1942.
63. Du Vigneaud, V., Chandler, J. P., Cohn, M., and Brown, G. B. The transfer of the methyl group from methionine to choline and creatine. *J. Biol. Chem.* 134:787, 1940.
64. Du Vigneaud, V., Chandler, J. P. Moyer, A. W., and Keppel, D. M. The effect of choline on the ability of homocystine to replace methionine in the diet. *J. Biol. Chem.* 131:57, 1939.
65. Du Vigneaud, V., Chandler, J. P., Simmonds, S., Moyer, A. W., and Cohen, M. The role of dimethyl- and monomethylaminoethanol in transmethylation reactions in vivo. *J. Biol. Chem.* 164:603, 1946.
66. Du Vigneaud, V., Simmonds, S., Chandler, J. P., and Cohn, M. A further investigation of the role of betaine in transmethylation reactions in vivo. *J. Biol. Chem.* 165:639, 1946.
67. Engel, R. W. Modified methods for the chemical and biological determination of choline. *J. Biol. Chem.* 144:701, 1942.
68. Engel, R. W. The choline content of animal and plant products. *J. Nutrition* 25:441, 1943.
69. Entenman, C., and Chaikoff, I. L. Is choline the factor in the pancreas that prevents fatty livers in depancreatized dogs maintained with insulin? *J. Biol. Chem.* 138:477, 1941.
70. Erickson, B. N., Avrin, I., Teague, D. M., and Williams, H. H. Micromethods for the determination of sphingomyelin and choline. Applications for the estimation of the phospholipid partition in blood and tissues. *J. Biol. Chem.* 135:671, 1940.
71. Ewins, A. J. Acetylcholine, a new active principle of ergot. *Biochem. J.* 8:44, 1914.

72. Fisher, N. F. Attempts to maintain life of totally pancreatectomized dogs indefinitely by insulin. *Am. J. Physiol.* 67:634, 1924.

73. Fleming, R. G., and Snell, A. M. Portal cirrhosis with ascites; analysis of 200 cases with special reference to prognosis and treatment. *Am. J. Digest Dis.* 9:115, 1942.

74. Fletcher, J. P., Best, C. H., and Solandt, O. M. The distribution of choline. *Biochem. J.* 29:2278, 1935.

75. Fouts, P. J. Vitamin B complex studies in dogs; production of cirrhosis of liver. *J. Nutrition* 25:217, 1943.

76. Glick, D. Concerning the reineckate method for the determination of choline. *J. Biol. Chem.* 156:643, 1944.

77. Goldstein, M. R., and Rosahn, P. D. Choline and inositol therapy of cirrhosis of the liver. *Connecticut M. J.* 9:351, 1945.

78. Griffith, W. H. The relation of choline to the kidneys. *Biol. Symposia,* 5:193, 1941.

79. Griffith, W. H., and Wade, N. J. Choline metabolism: II., The interrelationship of choline, cystine and methionine in the occurrence and prevention of hemorrhagic degeneration in young rats. *J. Biol. Chem.,* 132:627, 1940.

80. Guggenheim, M. Die Biogenen Amine (ed. 3). Basel, S. Karger, 1940.

81. György, P., and Goldblatt, H. Hepatic injury on a nutritional basis in rats. *J. Exper. Med.* 70:185, 1939.

82. György, P., and Goldblatt, H. Experimental production of dietary liver injury in rats. *Proc. Soc. Exper. Biol. & Med.* 46:492, 1941.

83. Handler, P. Dietary factors in the regulation of liver lipid concentration. *J. Biol. Chem.* 162:77, 1946.

84. Handler, P. Determination of choline in biological material. *Biol. Symposia* 12:361, 1947.

85. Handler, P., and Dann, W. J. The inhibition of rat growth by nicotinamide. *J. Biol. Chem.* 146:357, 1942.

86. Hershey, J. M. Substitution of lecithin for raw pancreas in the diet of the depancreatized dog. *Am. J. Physiol.* 93:657P, 1930.

87. Hershey, J. M., and Soskin, S. Substitution of "lecithin" for raw pancreas in the diet of the depancreatized dog. *Am. J. Physiol.* 98:74, 1931.

88. Hoagland, C. L., and Shank, R. E. Infectious hepatitis; review of 200 cases. *J.A.M.A.* 130:615, 1946.

89. Horowitz, N. H., and Beadle, G. W. A microbiological method for the determination of choline by use of a mutant of neurospora. *J. Biol. Chem.* 150:325, 1943.

90. Horowitz, N. H., Bonner, D., and Houlahan, M. B. The utilization of choline analogues by cholineless mutants of neurospora. *J. Biol. Chem.* 159:145, 1945.

91. Inukai, F., and Nakahara, W. Isolation of phosphocholine from beef liver. *Proc. Imp. Acad., Tokyo* 11:260, 1935.

92. Jacobi, H. P., Baumann, C. A., and Meek, W. J. The choline content of rats on various choline-free diets. *J. Biol. Chem.* 138:571, 1941.

93. Johnson, B. C., Hamilton, T. S., and Mitchell, H. H. The effect of choline intake and environmental temperature on the excretion of choline from the human body. *J. Biol. Chem.* 159:5, 1945.

94. Jones, C. M. Treatment of acute hepatic insufficiency and its relation to prognosis. *Am. J. Digest Dis.* 3:624, 1936.

95. Jukes, T. H. Choline. *Ann. Rev. Biochem.* 16:193, 1947.

96. Kahane, E. and Levy, J. Enzymic hydrolysis of acetylcholine by serum. *Compt. Rend. Acad. d. Sci.* 202:2186, 1936.

97. King, E. J., and Aloisi, M. Phosphoric esters of the pancreas; choline glycerophosphate. *Biochem. J.* 39:470, 1945.

98. King, E. J., and Small, C. W. Phosphoric esters of the pancreas: sphingosine choline phosphate. *Biochem. J.* 33:1135, 1939.

99. Klein, G., and Linser, H. Cholinstoffwechsel bei Pflanzen. *Biochem. Ztschr.* 250:220, 1932.

100. Landau, R. L., and Welch, A. D. The arsenic analogue of choline as a component of lecithin in rats fed arsenocholine chloride. *Federation Proc.* 1:156, 1942.

101. Lang, J. M., and Lucas, C. C. Unpublished data.

102. Levene, P. A., and Rolf, I. P. Note on the preparation of cephalin. *J. Biol. Chem.* 74:713, 1927.

103. Lewis, H. B. The metabolism of sulphur: IX., The effect of repeated administration of small amounts of cystine. *J. Biol. Chem.* 65:187, 1925.

104. Lillie, R. D., Daft, F. S., and Sebrell, W. H., Jr. Cirrhosis of liver in rats on deficient diet and effect of alcohol. *Pub. Health Rep.* 56:1255, 1941.

105. Lintzel, W., and Monasterio, G. A method for the microdetermination of lecithin in blood and plasma. *Biochem. Ztschr.* 241:273, 1931.

106. Lucas, C. C. Unpublished data.

107. Luecke, R. W., and Pearson, P. B. The microbiological determination of free choline in plasma and urine. *J. Biol. Chem.* 153:259, 1944.

108. Lundquist, F. Studies on the biochemistry of human semen. I. The natural substrate prostatic phosphatase. *Acta physiol. Scandinav.* 13:322, 1947.

109. McArthur, C. S. Biological incorporation of a choline homologue into liver phospholipids. *Science* 104:222, 1946.

110. McArthur, C. S., Lucas, C. C., and Best, C. H. The mode of action of lipotropic agents; proof of the in vivo incorporation of triethyl-β-hydroxyethyl-ammonium hydroxide into the phospholipid molecule. *Biochem. J.*, 41:612, 1947.

111. McIntire, J. M., Schweigert, B. S., and Elvehjem, C. A. The choline and pyridoxine content of meats. *J. Nutrition* 28:219, 1944.

112. Maclean, H., and Maclean, I. S. Lecithin and Allied Substances. London, Longmans, 1927.
113. Man, E. B., Kartin, B. L., Durlacher, S. H., and Peters, J. P. Lipids of serum and liver in patients with hepatic diseases. *J. Clin. Investigation* 24:623, 1945.
114. Marenzi, A. D., and Cardini, C. E. The colorimetric determination of choline. *J. Biol. Chem.* 147:363, 1943.
115. Marfori, P., de Nito, G., and Aurisicchio. Ueber die chemischen Eigenschaften des aktiven Prinzips der Lymphdrüsen (Lymphoganglin). *Biochem. Ztschr.* 270:219, 1934.
116. Moosnick, F. B., Schleicher, E. M., and Peterson, W. E. Progressive pernicious anemia successfully treated with intravenous choline chloride. *J. Clin. Investigation* 24:278, 1945.
117. Morrison, L. M. Response of cirrhosis of liver to an intensive combined therapy. *Ann. Int. Med.* 24:465, 1946.
118. Morrison, L. M. New methods of therapy in cirrhosis of the liver. *J.A.M.A.* 134:673, 1947.
119. Moyer, A. W., and du Vigneaud, V. The structural specificity of choline and betaine in transmethylation. *J. Biol. Chem.* 143:373, 1942.
120. Mulford, D. J., and Griffith, W. H. Choline metabolism: VIII., The relation of cystine and of methionine to the requirement of choline in young rats. *J. Nutrition* 23:91, 1942.
121. Newburgh, L. H., and Marsh, P. L. Renal injuries by amino acids. *Arch. Int. Med.* 36:682, 1925.
122. Paal, H. Hydrolysis of lecithin. *Biochem. Ztschr.* 211:244, 1929.
123. Patek, A. J., Jr. Treatment of alcoholic cirrhosis of the liver with high vitamin therapy. *Proc. Soc. Exper. Biol. & Med.* 37:329, 1937.
124. Patek, A. J., Jr. Dietary treatment of Laennec's cirrhosis, with special reference to early stages of the disease. *Bull. New York Acad. Med.* 19:498, 1943.
125. Patek, A. J., Jr. An evaluation of dietary factors in the treatment of Laennec's cirrhosis of the liver. *J. Mt. Sinai Hosp.* 14:1, 1947.
126. Patek, A. J., Jr., and Post, J. Treatment of cirrhosis of the liver by a nutritious diet and supplements rich in vitamin B complex. *J. Clin. Investigation* 20:481, 1941.
127. Pénau, H., and Simmonet, H. Insulin and experimental diabetes. *Ann. Méd.* 19:401, 1926.
128. Platt, A. P., and Porter, R. R. Influence of choline and ethanolamine on the rate of formation of phospholipids in the liver. *Nature* 160:905, 1947.
129. Rhian, M., Evans, R. J., and St. John, J. L. The choline content of feeds. *J. Nutrition* 25:1, 1943.
130. Rich, A. R., and Hamilton, J. D. The experimental production of cirrhosis of the liver by means of a deficient diet. *Bull. Johns Hopkins Hosp.* 66:185, 1940.

131. Richardson, J. S., and Suffern, W. S. Therapeutic trial of choline chloride in infective hepatitis. *Brit. M. J.* 2:156, 1945.

132. Roman, W. A chemical method for the determination of choline and some physicochemical data on choline and its salts. *Biochem. Ztschr.* 219:218, 1930.

133. Rose, W. C., and Rice, E. E. The utilization of certain sulfur-containing compounds for growth purposes. *J. Biol. Chem.* 130:305, 1939.

134. Rosenfeld, G. Fettbildung. *Ergebn. Physiol.* 2:50, 1903.

135. Russakoff, A. H., and Blumberg, H. Choline as an adjuvant to the dietary therapy of clinical cirrhosis of the liver. *Ann. Int. Med.* 21:848, 1944.

136. Schmidt, G., Hershman, B., and Thannhauser, S. J. The isolation of α-glycerylphosphorylcholine from incubated beef pancreas, its significance for the intermediary metabolism of lecithin. *J. Biol. Chem.* 161, 523, 1945.

137. Sellers, E. A., Lucas, C. C., and Best, C. H. The lipotropic factors in experimental cirrhosis. *Brit. M. J.* 1:1061, 1948.

138. Sharpe, J. S. Estimation of choline in blood. *Biochem. J.* 17:41, 1923.

139. Shaw, F. H. Estimation of choline and acetylcholine. *Biochem. J.* 32:1002, 1938.

140. Simmonds, S., Cohn, M., Chandler, J. P., and du Vigneaud, V. The utilization of the methyl groups of choline in the biological synthesis of methionine. *J. Biol. Chem.* 149:519, 1943.

141. Smyth, D. H. A water-soluble precursor of choline in the human placenta. *Biochem. J.* 29:2067, 1935.

142. Spellberg, M. A., and Keeton, R. W. The production of fatty and fibrotic livers in guinea pigs and rabbits by seemingly adequate diets. *Am. J. M. Sc.* 200:688, 1940.

143. Spellberg, M. A., Keeton, R. W., and Ginsberg, R. Dietary production of hepatic cirrhosis in rabbits. *Arch. Path.* 33:204, 1942.

144. Staněk, V. Über die quantitative Bestimmung von Cholin und Betain in Pflanzlichen Stoffen und einige Bemerkungen über Lecithine. *Ztschr. f. physiol. Chem.* 48:334, 1906.

145. Strack, E., and Schwaneberg, H. Über die Bestimmung von Basen aus tierischen Geweben. *Ztschr. f. physiol. Chem.* 245:11, 1936-37.

146. Strecker, A. Beobachtungen über die Galle verschiedener Thiere. *Ann. d. Chem.* 70:149, 1849.

147. Strecker, A. Über einige neue Bestandtheile der Schweinegalle. *Ann. d. Chem.* 123:353, 1862.

148. Tarver, H., and Schmidt, C. L. A. The conversion of methionine to cystine; experiments with radioactive sulfur. *J. Biol. Chem.* 130:67, 1939.

149. Tucker, H. F., and Eckstein, H. C. The effect of supplementary methionine and cystine on the production of fatty livers by diet. *J. Biol. Chem.* 121:479, 1937.

150. Tucker, H. F., and Eckstein, H. C. The effect of supplementary lycine, methionine and cystine on the production of fatty livers by high fat diets containing gliadin. *J. Biol. Chem.* 126:117, 1938.

151. Tucker, H. F., Treadwell, C. R., and Eckstein, H. C. The effect of supplementary cystine and methionine on the production of fatty livers by rats on high-fat diets containing casein or edestin. *J. Biol. Chem.* 135:85, 1940.

152. Watson, J., and Castle, W. B. Failure of choline chloride to augment anemia in cirrhosis of liver. *J.A.M.A.* 129:802, 1945.

153. Webster, G. T. Dietary liver disease in rats. *J. Clin. Investigation* 20:440, 1941.

154. Webster, G. T. Cirrhosis of the liver among rats receiving diets poor in protein and rich in fat. *J. Clin. Investigation* 21:385, 1942.

155. Welch, A. D. Utilization of the arsenic analogue of choline chloride in the bio-synthesis of phospholipid. *Proc. Soc. Exper. Biol. & Med.* 35:107, 1936.

156. Welch, A. D. The preparation of a casein hydrolyzate for the study of the relationship between choline and homocystine. *J. Biol. Chem.* 137:173, 1941.

157. Welch, A. D., and Landau, R. L. The arsenic analogue of choline as a component of lecithin in rats fed arsenocholine chloride. *J. Biol. Chem.* 144:581, 1942.

158. Welch, M. S., and Welch, A. D. Relation between size of dose and lipotropic effect of choline chloride in mice. *Proc. Soc. Exp. Biol. & Med.* 39:5, 1938.

159. Winzler, R. J., and Meserve, E. R. Spectrophotometric determination of small amounts of choline. *J. Biol. Chem.* 159:395, 1945.

160. Witts, L. J. Review of the dietetic factors in liver disease. *Brit. M. J.* 1:1; 45, 1947.

161. Woolley, D. W., and Peterson, W. H. The chemistry of mold tissue: xiv., Isolation of cyclic choline sulfate from aspergillus sydowi. *J. Biol. Chem.* 122:213, 1937.

162. Wurtz, A. Synthèse de la nevrine. *Comptes rendus,* 65:1015, 1867.

Chapter 23

VITAMIN C MALNUTRITION AND SCURVY

Frederick F. Tisdall and Norman Jolliffe

Centuries before the word *vitamin* was coined there were numerous references in the literature to outbreaks of a malady which is now referred to as scurvy. This disease, when it struck at large population groups, occurred when vegetation was scarce, when crops failed, when the choice of foods was restricted or when fresh food was unavailable. Probably the first description of undoubted scurvy was that of De Joinville, who accompanied the Crusaders in the thirteenth century. He stated that "Barber surgeons were forced to cut away the dead flesh from the gums to enable the people to masticate their food."[5]

The disease in the past frequently occurred amongst sailors who on long voyages to the Americas or around the world subsisted largely on salt meat and biscuits, with no fresh fruit or vegetables. They thus received diets which we now know were devoid of vitamin C. In those days, when the world was largely uncharted, it was thought that the distant seas were inhabited by various types of sea monsters. Terrible as these dangers seemed at that time, they were not as dangerous as scurvy.

During the latter half of the sixteenth century, Sir Richard Hawkins stated that in his twenty years at sea he had seen about 10,000 mariners destroyed by this disease. Lord Anson's Voyage of 1740–44 furnishes one of the notable examples of the ravages of scurvy in sailors before means of prevention were learned. Lord Anson sailed from England on November 4, 1740, with six ships manned by 961 men. By the time (June 1741) he reached the southwest coast of South America he had lost two-thirds of his crew and had abandoned three ships as a result of scurvy. By November of the same year scurvy had so reduced his crew that he abandoned two more ships. He returned to England on June 15, 1744, with more than four-fifths of his crew and five of his six ships lost through scurvy.

Of particular interest is the report made by Jacques Cartier in 1536.[2] During that year he wintered with his crew in the St. Lawrence River opposite what is now the city of Quebec. He states that out of 110 men forming his company, no less than 100 were sick. It is obvious from his description of the sick men that they were suffering from scurvy. One day he caught sight of an Indian whom he had seen ten or twelve days previously, extremely ill with the very disease from which his own men were suffering. The Captain enquired of this Indian what had cured his sickness. The Indian replied that he had been healed by the juice of the leaves of a tree and showed him how to grind the bark and leaves and make a brew or tea from them. After drinking this brew for a few days, Jacques Cartier's company recovered from their sickness. He states, "In less than eight days a whole pine tree—as large, as tall as any I ever saw—was used up and produced such a result that had all the doctors of Louvaine been there with all the drugs of Alexandria, they could not have done so much in a year as did this tree in eight days." We know that a brew of pine needles and pine bark made in this fashion contains a considerable quantity of ascorbic acid.

The role of fresh vegetables and fruit in the prevention of scurvy was noted as early as 1734 by Bachstrom. In that year he wrote as follows:

> This evil is solely owing to a total abstinence from fresh vegetable food, and greens; which is alone the true primary cause of the disease. And where persons, either through neglect or necessity, do refrain for a considerable time from eating the fresh fruits of the earth, and greens, no age, no climate or soil, are exempted from its attack. Other secondary causes may likewise concur: but recent vegetables are found alone effectual to preserve the body from this malady; and most speedily to cure it, even in a few days, when the case is not rendered desperate by the patient's being dropsical or consumptive.[5]

This formulation seems to be the first clear-cut statement of the cause of scurvy. It is also the first clear-cut statement that the lack of certain foods may cause disease. In it Bachstrom left behind the humor concept of disease, which still beguiled all of his contemporaries and pronounced for the first time a theory that disease could be caused by a lack of a specific type of food.

In 1752, James Lind, an English naval surgeon, crystallized in a classic treatise the concept of scurvy as a disease that could be cured by food alone. Of citrus fruit he wrote, "They contain something that neither medicine, surgery or physic could supply."[5] It was he who established the sound principles of the prevention and treatment of scurvy and devised a practical method for its effective use at sea. In 1795, a year after Lind's death, an Admiralty order was issued which required a regular ration of lemon juice for all members of the fleet, after which time scurvy disappeared from the British navy.

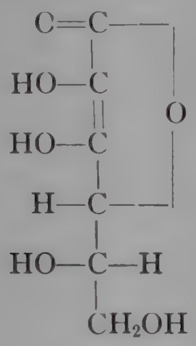
Epidemic scurvy occurred in adults largely under the special circumstances just noted. However, the same disease occurred with considerable frequency in infancy. Glisson,[4] in 1650, described scurvy in infancy, but confused it with acute rickets. It remained for Sir Thomas Barlow,[1] in 1883, to prove that scurvy in early life presented the same anatomic picture as adult scurvy. Beginning in 1912 physicians in Europe and America, particularly pediatricians, began to note, in children under one year of age, a new disease. In spite of Barlow's contribution, which had gone largely unrecognized, it was at first thought to be a particularly severe form of rickets. This was at the time when pasteurization of milk became widespread. With the destruction of tubercle bacilli and other pathogenic organisms by this process the small amount of ascorbic acid present in fresh cow's milk was also destroyed. The age of bacteriology had discovered the cause of many diseases and by pasteurization milk-borne infections of infants had been largely eliminated. This is an example of how real improvements in public health may be associated with undesirable side effects. The introduction of orange juice into the diet of young infants effectively eradicated the dangers of scurvy resulting from pasteurization of milk. Subsequent studies showed orange juice to be a more potent and dependable source of vitamin C than raw cow's milk.

In 1906 Hopkins[6] postulated that scurvy was a deficiency disease due to a lack of some essential food substance, the exact nature of which was not known. In 1907 Hölst and Frölich[11, 12] produced scurvy in guinea pigs, by feeding them restricted diets. The view that scurvy was a deficiency disease was again suggested by Funk in 1912. In 1915, McCollum and Davis,[8] working with the rat which does not require vitamin C in its diet, reported that not only was a substance essential for life present in fat but also a substance which was soluble in water. To differentiate between the two, the names *fat soluble A* and *water soluble B* were suggested by McCollum and Kennedy[9] in 1916, thus initiating the alphabetical nomenclature for the vitamins. The antiscorbutic vitamin was later designated as vitamin C.

Many unsuccessful attempts were made to isolate vitamin C. Finally, in 1928 Szent-Györgyi,[14] in studies on cellular oxidation, isolated "hexuronic acid" without knowing that it was vitamin C. In 1932 Waugh and King[15] isolated vitamin C from lemons and identified it with the "hexuronic acid" of Szent-Györgyi and showed it identical in antiscorbutic activity with vitamin C from orange juice. The structural formula of vitamin C was established by Hirst and his co-workers in 1933. In the same year Reichstein and his co-workers and Hirst and his co-workers almost simultaneously synthesized vitamin C. In 1933 Szent-Györgyi and Haworth suggested the name *ascorbic acid* for vitamin C. For a time the Council on Pharmacy and Chemistry of the American Medical Association adapted the non-functional designation, *cevitamic acid* as the official name and used it in its publications, but the Council finally (1939) abandoned *cevitamic acid* in favor of the name *ascorbic acid.*

CHEMISTRY

Vitamin C is a white crystalline substance freely soluble in water and ethyl alcohol and is a strong reducing agent.



In crystalline form and kept dry and not exposed to light, ascorbic acid is stable for a considerable time, and after two years in tropical climates there is practically no loss in potency. In solution the stability depends on many factors, being destroyed more rapidly in the presence of oxygen, catalysts such as iron and copper, high (alkaline) *p*H, and higher temperatures. In aqueous solution prepared with extreme care, the vitamin is reasonably stable at *p*H 7.6 or lower. Oxalic acid and metaphosphoric acid are good stabilizing agents.

PHYSIOLOGY

The best-established function of ascorbic acid is to maintain collagen formation, the so-called intracellular substances of certain mesenchymal tissues such as connective tissue, the osteoid tissue of the bones, and of the dentine of the teeth. Normally in the intracellular substance fibroblasts lie in an amorphous ground substance within which fibrils of reticulum are seen as wavy bands of collagen cemented together by a translucent matrix. In the scorbutic animal the ground substance and fibroblasts are unaffected but no collagen is formed. After administration of vitamin C bundles of collagenous material are formed within twenty-four hours. The mechanism through which ascorbic acid brings this about is unknown, but its effect on wound-healing, dentine, cartilage, and the matrixes of the bones is well known, and has been frequently described.[11, 16]

Though the hemorrhagic manifestation of vitamin C deficiency is one of its most constant symptoms, its cause is still unknown. It has been suggested, but not proved, that the increased fragility of the capillaries is also due to the defect in cement substance binding the capillary endothelium, or in the pericapillary connective tissue and collagen sheath. Actually the physiology and minute structure of the capillary wall is not well known.

For many years it has been known that vitamin C is a factor influencing the formation of hemoglobin and the maturation of the erythrocytes from the reticulo-endothelial cell to the adult erythrocyte. Anemia is frequent but not constantly present in human scurvy, and a reticulocyte response has resulted from ascorbic acid administration in scorbutic-anemic patients. Clinically a few cases of nutritional anemia have been reported to respond to ascorbic acid after failing to respond to iron. Cases of macrocytic anemia have been reported which failed to respond to either liver or iron, but responded to vitamin C therapy. It therefore seems probable that other factors, usually more directly responsible for hemoglobin formation and erythrocytic maturation, are not always or completely effective in the presence of ascorbic acid depletion.

In both infants and guinea pigs, vitamin C deficiency impairs the metabolism of tyrosine and phenylalanine. This leads to darkening of the urine by oxidation of the phenolic end products and can be corrected promptly by ascorbic acid administration.

Vitamin C deficiency also leads to a steady rise in respiratory exchange, at least in experimental animals, and there is evidence to support the same disturbance in human beings. This increase in respiratory rate has been demonstrated in vitro and in vivo, and represents a very fundamental and characteristic disturbance resulting from ascorbic acid deficiency.

A systemic relation of ascorbic acid intake to resistance against infection is indicated by controlled observations with experimental animals and by clinical observations. Since depletion of the vitamin reserves is accompanied by many derangements in cellular enzyme activity, the resultant lowered resistance to injury and infection is regarded as complex rather than specific in nature. A marked tendency toward infection of the gums, skin, and areas injured by trauma is fairly characteristic of scurvy in man, guinea pigs, and monkeys.

An increased requirement of vitamin C to prevent the characteristic lesions of scurvy has been demonstrated as a result of infections, as in tuberculosis and streptococcic infections of the upper respiratory tract. Injections of bacterial toxins have been shown to cause a marked lowering of the vitamin reserves in guinea-pig tissues, and the animals are more sensitive to injury when the vitamin intake is low.

REQUIREMENTS

The minimum amount of ascorbic acid required for the prevention of clinical scurvy in infants and adults has been estimated as between 5 mg. and 15 mg. daily. It has already been noted that there was an increased incidence of infantile scurvy when pasteurized milk was first introduced and before it was customary to include orange juice in the infant's diet. As the amount of milk usually consumed between the third and twelfth months of life varies from 425 to 850 Gm. daily, and as pasteurized milk contains about 0.7 mg. of ascorbic acid per 100 Gm., the amount of milk consumed would furnish from 3 to 6 mg. of ascorbic acid daily. This amount of ascorbic acid was thus not sufficient to prevent scurvy in all infants. Similarly, in adults 1020 to 1928 Gm. of pasteurized milk in ulcer diets, supplying from 7 to 11 mg. of ascorbic acid daily, is not sufficient to prevent scurvy. Larger amounts of ascorbic acid are required for chemical saturation.

A point of special interest is that nature provides to breast-fed infants amounts of ascorbic acid approximately that required for chemical saturation. On the basis that human milk from normally fed mothers supplies 5.2 mg. of ascorbic acid per 100 cc., and that the caloric intake of infants averages 100 calories per Kg. body weight, then infants between 3.6 and 7.2 Kg. (8 and 16 lb.) will obtain daily about 7.2 mg. of ascorbic acid per Kg. body weight.

The Daily Allowances of the National Research Council (Appendix Table A), set high enough to include most normal persons with above-average requirements are: for the average man or woman 75 mg.; for the latter half of pregnancy 100 mg.; for lactation, 150 mg.; for infants under 1 year, 30 mg.; for children 1 to 3 years, 35 mg.; for children 4 to 6 years, 50 mg.; for children 7 to 9 years, 60 mg.; for children 10 to 12 years, 75 mg.; for girls 13 to 20 years, 80 mg.; for boys 13 to 15 years, 90 mg.; and for boys 16 to 20 years, 100 mg. Requirements are increased in patients having hypermetabolism, whether caused by hyperthyroidism, fever either artificially produced or by infections, or by cellular proliferation as in malignant disease and leukemia.

PATHOLOGY

The pathology of scurvy in the human being has been shown to be identical with that found in the experimental animal. As noted previously the cause of the increased capillary fragility is unknown, and the pathology of these manifestations is that resulting from blood extravasations into the various tissues.

The pathologic changes that occur in the bones result in the characteristic evidences of the disease described by roentgen examination. In common with rickets, the changes are most marked where the bones are growing rapidly, such as the sternal ends of the middle ribs, the lower end of the femur, the upper ends of the tibia and fibula, the upper end of the humerus, and the lower ends of the radius and ulna. In the formation of normal bone, columns of cartilage cells are laid down regularly at the ends of the growing bones. These columns are surrounded by matrix. In scurvy, the columns tend to be irregular. In the normal bone, as the cartilage cells degenerate, capillaries grow into these columns and lay down lime salts in the surrounding matrix. Osteoblasts are then laid down on certain masses of the calcified matrix to form trabeculae, or true bone tissue, and the remaining portion of the calcified matrix is promptly removed and replaced by marrow tissue. In scurvy, there is interference with the removal of the calcified matrix, which piles up at the end of the growing bone. In spite of the amount of calcium in this matrix, it tends to be quite brittle. Also in scurvy there is diminished formation of new trabeculae, while resorption of trabeculae already formed proceeds at the normal rate. These changes reduce the strength of the bone and fractures frequently occur, particularly near the ends of the long bones. These bone changes so typical of scurvy in the infant may not be evident in adult scurvy, though hemorrhages subperiosteally and into and about the joints do occur. The dentine of the teeth becomes porotic and resorption occurs along Tomes' canals. Loosening and falling out of the teeth is due to rarefaction of the alveolar process.

CLINICAL MANIFESTATIONS

The clinical picture of scurvy is so modified by growth that it is necessary to describe the picture separately in infants and adults.

INFANTILE SCURVY

Infantile scurvy occurs only in artificially fed infants except under most unusual circumstances. In Austria after the First World War, when many mothers were receiving a diet practically devoid of vitamin C, the occurrence of infantile scurvy in their offspring was noted.

In regard to the age incidence, the records of the Hospital for Sick Children, Toronto, indicate that 3 out of 4 infants suffering from scurvy are between 6 and 12 months of age. The youngest infant with scurvy encountered at the Hospital was 5 months of age. Only 4 per cent of the infants with scurvy were over 2 years of age.

The clinical picture of infantile scurvy is usually clear-cut. A history frequently obtained is that the infant has been irritable with failing appetite and loss of weight for the previous ten to fourteen days. The first symptom that makes an impression on the mother is that the baby cries on being handled, particularly when it is being elevated by the ankles to change the diaper. The infant usually lies on his back and makes no attempt to move one or both legs, and sometimes, in addition, one or both arms. Lifting or moving the child obviously causes severe pain. Tenderness of the extremities and pain on movement are almost invariably present. Hemorrhages may occur anywhere in the body and are due to an increased permeability or fragility of the blood vessels. They occur most frequently under the periosteum of the long bones, in the gums, the skin, and the mucous membranes. Bleeding occurs under the periosteum of the long bones in approximately two-thirds of infants with scurvy. It occurs most frequently at the lower end of the femur (see XII*c* and d, p. 101), followed by the upper end of the humerus. It occurs much less frequently at the ankles and the wrists. The stripping up of the periosteum by the hemorrhage under it may be so great that along with concurrent edema definite swelling may be evident on clinical examination. Of considerable diagnostic importance is the exact location of this swelling. Due to the fact that the periosteum of the long bones fuse with the perichondrium near the ends, the swelling cannot extend beyond the bone end. The long bone thus has the shape of a club. Careful examination discloses that the swelling does not involve the joint.

Hemorrhage under the mucous membranes of the gums also occurs in approximately two-thirds of the infants with scurvy. They are frequently swollen, tense, and a dark red color (see IV*e*, p. 69). Swelling usually appears in the gingival tissue around the erupted teeth, although in certain instances swelling will occur before the eruption of the teeth. If both the upper and the lower incisors have erupted, the gum changes are more marked in the upper gums, the swelling being so great that the teeth may be almost entirely covered by the swollen gums.

Hemorrhage into the skin is seen in about one-third of the cases. It usually occurs as a result of some slight stress, such as a slight knock or constriction. Petechiae may be scattered over the skin and occasionally on the mucous membranes of the mouth. Ecchymotic areas on the skin may also be present (see IV*c* and *d*, p. 69).

Evidence of bleeding in the stools, urine, and vomitus is infrequently seen.

Enlargement of the costochondral junction (the scorbutic rosary) (see XV*a*, p. 113) occurs in three-fourths of scorbutic infants; in fact, in order of frequency it is second only to tenderness of the extremities. As one follows the ribs from the axillary line forward towards the sternum, a definite enlargement can be felt at the junction of the rib with the cartilage. Frequently as the disease progresses a sharp depression or angle can be felt as though the whole sternum and the attached cartilage had been pushed slightly backward. This is due to the development of fractures. In rickets the enlargement of the costochondral junction is always rounded.

A slight elevation of temperature is frequently found in scurvy, usually ranging from 100° to 102° F. With treatment, the temperature usually returns to normal in two to seven days. Along with the elevation in temperature, there is an increase in the pulse and respiratory rates.

Probably because of involvement of the bone marrow and the increased tendency to hemorrhage, infantile scurvy is usually accompanied by a mild secondary anemia. This secondary anemia frequently responds to antiscorbutic treatment alone.

The roentgen changes in scurvy, when all are present, are so characteristic that they are diagnostic of the disease. At the ends of the long bones (metaphyses) there is a transverse band of increased density sometimes referred to as the "white line of scurvy." This is due to piling up of the calcified matrix. On the shaft side of these white lines a localized transverse band of rarefaction sometimes appears. The transverse rarefied band tends to make the "white lines" more prominent radiologically. This band first becomes evident at the lateral margins of the shaft and appears as a small nick or cleft in the bone. Fractures frequently occur at the zone of rarefaction and indeed may occur through the thickened epiphyseal plate ("white lines"). If the fracturing is severe enough the epiphyses may be displaced to one or other side of the shaft or may be mushroomed into the shaft giving a "ball and socket" appearance, with spur formation at the lateral margins of the shaft. During the healing process similar spurring may occur, it being the earliest sign of new bone formation under the stripped-up periosteum. The epiphyses exhibit a "halo" appearance which is due to the increased calcification at the growing circumference together with central epiphyseal rarefaction.

As the result of thinning and reduction of the number of trabeculae throughout the shaft there is a generalized increase in transparency with the trabecular markings being indistinct. The cortex is thinned out and the bony framework presents a "ground-glass" appearance.

These then are the roentgen changes which may be present in infantile scurvy:

1. Thickening of the epiphyseal plate or "white line" at the ends of long bones;
2. "Halo" appearance of epiphyses;
3. Zone of rarefaction immediately shaftward to the "white line";
4. Separation of the epiphysis;
5. Spur formation;
6. "Ground-glass" appearance of the shaft;
7. Thinning of the cortex.

No one of these changes is characteristic of the disease but together they form a picture which need not be mistaken for any other condition.

The most frequent site for hemorrhage in scorbutic infants is under the periosteum of the long bones. The periosteum is attached at the growing ends of the bones. Because of the slight stress of moving the infant, such as picking it up to change its diaper, fractures which occur at the zone of rarefaction not only cause the tenderness of the extremities as seen in almost every case of scurvy but may also cause bleeding underneath the periosteum. This causes the periosteum to be stripped up and produces a clublike swelling extending from the end to past even the middle of the shaft. As the periosteum is attached to the end of the shaft, the swelling never extends into the joint. Because of lack of osteoblastic activity, with resultant lack of formation of osseous tissue, the stripped-up periosteum does not cast a shadow on roentgenographic examination until ascorbic acid therapy has been given from seven to ten days. At the end of this time calcium is laid down in the hemorrhage under the periosteum, casting a dense shadow and "cloaking" the shaft in a solid, dense calcified mass. As treatment proceeds this mass is absorbed and the shaft returns to normal and if the epiphysis has been displaced the shaft realigns itself to this displaced center (see XII*d*, p. 101).

In addition to the roentgen changes involving the bone, soft-tissue changes are frequently visualized. These are interpreted as being due to soft tissue edema or hemorrhage.

DIFFERENTIAL DIAGNOSIS

Infantile scurvy is sometimes incorrectly diagnosed as rheumatic arthritis, probably because of the tenderness and swelling at the ends of the long bones. Careful examination reveals that the swelling does not involve the joints. Rheumatic infection is rare under 2 years of age, while infantile scurvy is rare over 2 years of age. In infants under 4 months of age syphilis may cause tenderness of the extremities, but scurvy is rare under 6 months of age. Due to lack of movement of the extremities with scurvy an incorrect diagnosis of infantile paralysis is sometimes made.

LABORATORY FINDINGS

As the etiologic factor in the production of scurvy is the lack of ascorbic acid, the disease only develops when the body stores of ascorbic acid have been exhausted. In the average normal infant the fasting plasma ascorbic acid level is above 0.6 mg. per 100 cc. In scurvy the level is almost always zero. However, a zero plasma ascorbic acid level does not mean the infant has scurvy. If an individual is placed on an ascorbic-acid-free diet the blood level rapidly diminishes and after three to six weeks the plasma level drops to zero. However, it takes some months before the tissues are depleted and scurvy develops. Thus, while a zero or near zero plasma level is always present in a patient with scurvy, its presence only indicates that the patient has been on an ascorbic acid free diet for the previous three to six weeks. Also, a fasting plasma ascorbic acid level lower than 0.6 mg. per 100 cc. usually indicates that the patient has been receiving for the preceding few weeks an insufficient quantity of ascorbic acid to saturate the body tissues.

Adult Scurvy

Adult scurvy of the type so vividly described during the sailing ship era is today infrequent though almost every large general hospital will admit a few cases each year. Outside the indigent, the insane, the alcoholic, and the food faddist most subjects with clinical adult scurvy who are admitted to hospitals have the deficiency because of some therapeutic diet consisting chiefly of milk and cereals and usually containing less than 15 mg. daily of ascorbic acid. This type of diet, especially when used in conjunction with antiacids and when not properly supplemented may within several months produce clinical scurvy.

Manifest scurvy in adults is preceded as a rule by lassitude, weakness, irritability, vague muscle or joint aches and pains, and a loss of weight.

Bleeding gums (see IV*f*, p. 69), gingivitis, and loosening of the teeth are usually the earliest objective signs. During this period metabolic stress such as infection is apt to precipitate the clinical picture. Here hemorrhagic manifestations predominate. Stress or mild trauma too slight to be remembered usually determines their site, as for example the trauma of the blood pressure cuff (IV*b*) or tourniquet, a slight pinch, or the pressure from shoes (IV*c*). Large muscle hemorrhages, particularly in the thigh muscles, are common, as are petechiae and purpura (IV*d*). Perifollicular congestion (IV*a*) particularly in the dependent portions of the body, is frequent. Rapidly developing hemorrhages into the gingivae are common giving the gums the appearance of bags of blood. Slight pressure will rupture them, often causing profuse but not dangerous bleeding. Epistaxis, conjunctival, retinal, cerebral, gastrointestinal, and genitourinary bleeding all occur, but are rare except in severe cases. The bone lesions, except for the subperiosteal hemorrhages described in infantile scurvy, do not occur in the adult. Intercranial bleeding is not common.

LABORATORY FINDINGS

In manifest adult scurvy prior to treatment or the intake of ascorbic-acid-containing foods, the plasma ascorbic acid is usually zero though occasionally traces may be present. Many people without scurvy have levels of plasma ascorbic acid levels of 0 to 0.3 mg. per 100 cc., so the blood levels are not diagnostic of scurvy but indicate only recent intake or blood transport at the time the blood was drawn. Ascorbic acid levels in the white cell-platelet layer of the centrifuged blood is more significant and levels below 0.1 mg. per 100 cc. have a close correlation with the presence of scurvy. When storage of vitamin C has been depleted very little ascorbic acid appears in the urine and most of a test dose is retained. This test again does not tell if scurvy is present, but only indicates depletion of the reserves. Increased capillary fragility is an almost constant finding in scurvy though negative tests do occur in subjects having undoubted scurvy and several other conditions give a positive test. The slow disappearance of the dye, 2, 6-dichlorphenolindophenol when injected intracutaneously is only indicative of tissue depletion of ascorbic acid. Hypochromic anemia, not due to blood loss, is a common finding. The total and differential white blood cell counts are normal in uncomplicated subjects. The platelets are not decreased. Bleeding, coagulation, and prothrombin times are usually normal though in very severe cases the first two may be slightly prolonged. There may be changes in the serum calcium-phosphorus levels, but they are inconstant.

DIFFERENTIAL DIAGNOSIS

Adult scurvy must be differentiated from various forms of arthritis, diseases giving hemorrhagic manifestations, and from many forms of acute and chronic gingivitis. In adult scurvy the joint symptoms are due to hemorrhages around or sometimes into the joint. The presence of hemorrhagic manifestations elsewhere and blood chemical and hematologic studies are aids. The gingivae in classical scurvy appear to consist of bags of blood which rupture on slight pressure. If caused by scurvy, a therapeutic trial will result in obvious improvement within seventy-two hours or less, with absorption of most of the blood and edema fluid in the gingivae within a week. In more chronic gingivitis due to vitamin C deficiency superimposed infection and calculae prevent rapid response and ascorbic acid therapy results in slow improvement over several months.

In both infantile and adult scurvy the elimination of other causes of the hemorrhagic manifestations and the presence of very low or absent plasma or white cell-platelet layer ascorbic acid levels are important diagnostic aids.

ASCORBIC ACID DEFICIENCY WITH INCOMPLETE SCURVY

Though clinical scurvy is rare in this country, signs of ascorbic acid deficiency are undoubtedly more common but so nonspecific that their interpretation without laboratory studies and a therapeutic trial are extremely precarious. Impaired wound healing, gingivitis, follicular congestion with or without follicular hyperkeratosis, increased capillary fragility, purpura, petechiae, and hematomas can all occur singly in ascorbic acid deficiency. Each can also be produced by other factors. Crandon,[7] who placed himself on a diet, ascorbic acid free, but presumably containing all the other essentials, has so well studied and reported on these findings that they will be reviewed in extenso here.

The plasma ascorbic acid rapidly fell and reached zero after forty-one days, where it remained through the rest of the study until ascorbic acid was administered. The white cell-platelet layer of the centrifugal blood fell much more slowly, being at a relatively normal level of 28 mg. per 100 cc. on the seventieth day, 4 mg. on the eighty-second day, and zero on the one hundred and twenty second day. During the first four months all the clinical findings were essentially negative, although there was a slight loss of weight, a fall in the basal metabolic rate, and some weakness and fatigue on exertion. The fatigue appeared at the beginning of the third month and became progressively more marked, and toward the end of the experiment performance on the treadmill was impaired, and running was only possible for sixteen seconds, equivalent to that of a man in his eighth decade. Relief from the fatigue and lassitude followed the administration of ascorbic acid within twenty-four hours.

After one hundred and thirty-four days skin lesions developed. These consisted of small hyperkeratotic papules over the buttocks and the posterior aspects of the calves. Each papule contained an ingrown hair which could be seen if the hyperkeratotic plug was scraped off. The skin was dry particularly over the exterior surfaces. After one hundred and sixty-one days both petechial and perifollicular hemorrhages appeared on the legs. After six months they were abundant and on the thighs replaced the hyperkeratotic papules. The administration of ascorbic acid rapidly cleared these lesions.

At the end of six months the gums were slightly edematous on pressure but no other gross changes were recorded. A biopsy of the gingivae showed normal tissue. There were minor changes in the lamina dura of the teeth as shown by the dental X-ray films.

The erythrocyte count showed no significant fall though there was a slight fall in hemoglobin during the third month which was corrected by ferrous sulphate. The white cell count remained around 5000 until after one hundred and thirty-two days, when it fell to 3500, and later to 3200. This mild leukopenia responded rapidly to vitamin C.

Capillary fragility was unchanged throughout the entire period of observation, as were the blood complement determinations. The basal metabolic rate fell to minus 22 per cent of normal, but this was attributed to the loss of weight and caloric undernutrition rather than to ascorbic acid deficiency. Insulin and glucose tolerance tests were normal. Gastric analysis showed a drop in both the free and total acidity, which returned to normal after ascorbic acid administration. X-ray films and electrocardiograms were normal.

At the end of 3 months a fairly large incision was made in the right midback. Ten days later a biopsy showed good healing and ample intercellular substance and capillary formation. A report of this procedure was made just after six months. Healing appeared to be progressing, but a biopsy ten days later showed that beneath the skin the wound was filled with an unorganized blood clot. Sections of the wound showed a lack of intercellular substance and capillary formation. Immediately after this latter biopsy 1000 mg. of ascorbic acid was administered parenterally, and ten days later another biopsy showed good healing and ample intercellular substance.

TREATMENT AND PREVENTION

The treatment is the administration of ascorbic acid. Infantile scurvy responds to therapy in a dramatic manner. The administration of 4 to 8 oz. of orange juice daily in divided doses (this amount of orange juice supplies 60 to 120 mg. of ascorbic acid), or 300 to 500 mg. of ascorbic acid in tablet form will cause the pain to subside in twenty-four to forty-eight hours, and the gums to show decreased redness, swelling, and tendency to bleeding within seventy-two hours. It is advisable to continue the administration of 4 to 8 ounces of orange juice daily for two or three weeks, after which the amount can be reduced to 2 to 3 ounces daily.

Infantile scurvy can be prevented by the administration of either orange juice or tomato juice, starting during the first month of life. One to 2 teaspoons of orange juice or tomato juice may be given once a day and the amount rapidly increased until the infant is receiving 30 c.c. of orange juice at 1 month of age and 60 c.c. at 3 months of age or triple these amounts of tomato juice. If for any reason the infant does not tolerate these substances, ascorbic acid may be given, 25 mg. daily to the small infant and 50 mg. daily to the larger infant.

The general treatment of adult scurvy will be outlined in Chapter 25. The specific treatment is the administration of ascorbic acid. During the first week 1000 mg. of ascorbic acid orally in divided doses are recommended. This amount can usually be halved in the second week and then continued until all signs have disappeared when the usual preventive doses can be given. When parenteral therapy is indicated one-half of the oral doses in the form of sodium ascorbate can be given intravenously or intramuscularly in divided doses. In some persons a combination of oral and parenteral therapy is indicated. When this is so the oral therapy as outlined above should be followed supplemented by 100 mg. of sodium ascorbate given intravenously or intramuscularly two or three times daily until the disease is under control. In all subjects general measures as indicated in Chapter 25 should be followed.

In incomplete scurvy as manifested by gingivitis, repeated hemorrhagic manifestations, or joint symptoms, 300 to 500 mg. of ascorbic acid daily in divided doses is advisable. This must be continued for months.

BIBLIOGRAPHY

1. Barlow, T. On cases described as acute rickets which are probably a combination of scurvy and rickets. *Medico-Chirurgical Trans.* 66:159, 1883.
2. Biggar, H. The Voyages of Jacques Cartier. Canadian Public Archives, Publication 11, p. 204, 1924.
3. Dunlap, D. M., and Scarborough, H. The specific effect of ascorbic acid on the anemia of scurvy. *Edinburgh M. J.* 42:476, 1935.
4. Glisson, F. De Rachitide sive Mrobo Puerite qui vulgo, "The Rickets" dicitur. London, 1650.
5. Hess, A. F. Scurvy Past and Present. Philadelphia, Lea 1920.
6. Hopkins, F. G. The analyst and the medical man. *Analyst* 31:395, 1906.

7. Lund, C. C., and Crandon, J. H. Human experimental scurvy. *J.A.M.A.* 116:663, 1941.

8. McCollum, E. V., and Davis, M. The influence of certain vegetable fats on growth. *J. Biol. Chem.* 21:179, 1915.

9. McCollum, E. V., and Kennedy, C. The dietary factors operating in the production of polyneuritis. *J. Biol. Chem.* 24:491, 1916.

10. Park, E. A., Guild, H. G., Jackson, D., and Bond, M. The recognition of scurvy with especial reference to the early X-ray changes. *Arch. Dis. Childhood,* 10:265, 1935.

11. Ralli, E. P., and Sherry, S. Adult scurvy and the metabolism of vitamin C. *Medicine* 20:251, 1941.

12. Ralli, E. P., Friedman, G. J., and Sherry, S. The vitamin C requirements of man: Prolonged study of daily excretion and plasma concentration of Vitamin C. *Proc. Soc. Exper. Biol. & Med.* 40:604, 1939.

13. Suirbely, J. L., and Szent-Györgyi, A. Hexuronic acid as the Antiscorbutic factor. *Biochem. J.*, 26:865, 1932.

14. Szent-Györgyi, A. On Oxidation, Fermentation, Vitamins, Health and Disease. Baltimore, Williams & Wilkins, 1939.

15. Waugh, W. A., and King, C. G. The chemical nature of vitamin C. *J. Biol. Chem.* 97:325, 1932.

16. Wolbach, S. B. Pathologic changes resulting from vitamin deficiency. *J.A.M.A.* 108:7, 1937.

Chapter 24

PYRIDOXINE, PANTOTHENIC ACID, BIOTIN, INOSITOL, AND VITAMIN E

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PYRIDOXINE

In 1934, György reported the existence of a nutritional factor for rats, which was distinct from other known members of the vitamin B complex. This factor was known as vitamin B_6, a deficiency of which, in rats, produced a scaling dermatitis with hyperkeratosis of the ears, paws, nose, mouth, and eyes, with edema of the underlying corium. Because of this lesion, which György named "rat acrodynia," the missing nutrient was called the "rat anti-dermatitis factor," "adermin," and the "antiacrodynia factor," but the name Pyridoxine suggested by György eventually won general recognition and was accepted in 1940 by the American Institute of Nutrition as the official designation for this vitamin.

Pyridoxine was first isolated in pure form in 1938 almost simultaneously by five different laboratories, and it was then synthesized the following year by the group at the Merck laboratories.[9] The availability of pure crystalline pyridoxine led very naturally to the hope and belief that its nutritional role in both experimental animals and humans would be quickly clarified. Although a reasonably clear-cut deficiency picture has been identified in some animals, we are still, a decade after the pure material first became available, uncertain of the role of this vitamin in human nutrition.

The natural occurrence of pyridoxine corresponds in general to the distribution of the vitamin B complex. The accompanying table shows its occurrence in several common foodstuffs. Among animal tissues, kidney and muscle are the richest sources, ranging from 20 to 30 mg. per 100 Gm. dry weight of tissue. Cod and salmon muscle are also rich in pyridoxine.

PYRIDOXINE CONTENT OF FOODS
(MICROGRAMS PER GRAM DRY WEIGHT)

Nitab (rice bran concentrate)	5.17
Yeast, Fleischmann's	3.95
Yeast, brewers'	2.47
Liver powder (Wilson)	1.45
Whole milk	1.25
Yeast extract	1.03
Wheat germ	1.03
Beef liver	0.81
Leg of lamb	0.45
Split peas	0.40
Skim milk powder	0.38
Quaker rolled oats	0.25

Attention has been focused during the past five years on attempts to identify the biochemical role of pyridoxine in metabolism. All of these studies indicate an important function in protein metabolism. One of the most interesting manifestations of this function relates to antibody production. It has been shown in rats that pyridoxine deficiency impairs the capacity to produce circulating antibodies to injected sheep erythrocytes.[16] Further extension of this work[1] has shown very clearly the importance of pyridoxine (and pantothenate) in antibody production. This line of investigation should now be extended to humans.

In addition to pyridoxine itself, two other forms of the vitamin have been prepared, each having a higher specific potency in some assay procedures than the original compound.[13] These are pyridoxamine and pyridoxal, both of which, in addition to their phosphorylated forms, occur in nature and are active in all biologic systems that have been studied. Phosphorylated pyridoxal appears to be a coenzyme, or prosthetic group for those enzymes which decarboxylate tyrosine, arginine, glutamic acid, "dopa," the precursor of melanin, and possibly other amino acids.[8] It is also active in catalyzing various transaminating reactions, by which amino groups are transferred from one compound to another.[17] In confirmation of these findings, the tissues of pyridoxine-deficient rats do not possess a normal capacity for performing these reactions.[2] In the normal metabolism of tryptophan, also, this vitamin is known to play an important role, since the fate of that amino acid is profoundly altered in pyridoxine deficiency. Lepkovsky and Neilsen[11] identified an abnormal pigment in the urine of pyridoxine-deficient rats, which was later found to be xanthurenic acid. Pyridoxine is known to be related to tryptophane intake, since its quantitative urinary excretion in these animals parallels the dietary fluctuations of that amino acid. In addition, Umbreit, Wood, and Gunsalus[18] have shown that pyridoxal phosphate functions in the formation of tryptophane from indole and serine. Thus the conclusion seems inescapable that pyridoxine functions in metabolism in an enzymatic mechanism for the degradation of protein, and, in its absence, these reactions are either slowed down or diverted into abnormal channels. Present evidence suggests that pyridoxal phosphate is the active compound into which all other forms of the vitamin are first converted.

Birch, György, and Harris[3] noted many years ago that the scaling skin lesions of rat acrodynia could be more easily produced with low-fat diets and more easily cured if fat, in addition to pyridoxine, was added to the diet. This "pyridoxine sparing action of fat" seemed to indicate some relationship of the vitamin to the metabolism of the unsaturated fatty acids. The details of this relationship have not been clarified up to the present time and it does not seem profitable to speculate upon the possible importance of these findings to clinical medicine.

Pyridoxine-deficient dogs and swine develop a microcytic, hypochromic anemia which cannot be cured by any form of therapy except the restoration of the missing vitamin to the diet.[6, 7] This anemia is accompanied by a sharp rise in serum iron, indicative of a failure in the normal synthesis of hemoglobin. Cartwright and Wintrobe[5] have recently shown a marked failure of protoporphyrin synthesis in pyridoxine-deficient swine, suggesting that defective porphyrin metabolism may be the key to this anemia. Restoration of pyridoxine to the ration induces an immediate and striking reticulocyte response with clearing of all manifestations. Hyperplasia of the bone marrow reverts to normal, but the hemosiderosis of liver, spleen, and bone marrow may persist.

Another defect produced by pyridoxine deficiency in animals is that reported by Reid and his co-workers[12] in cattle. Poor growth, anorexia, poor condition of the hair coat, and poikilocytosis develop when the diet is restricted, but restoration of pyridoxine produces complete remission.

It is natural that attempts to apply our present knowledge of pyridoxine to clinical medicine should be based upon the recognized deficiency states in experimental animals. Despite numerous studies, however, these attempts have invariably led to failure, and there does not exist at present a clinical syndrome which is generally recognized as pyridoxine deficiency.

The earliest attempts to use this vitamin in human deficiency disease were those of Spies and his associates[14] who described a syndrome characterized by weakness, nervousness, insomnia, irritability, abdominal pain, and difficulty in walking, which they believed to be due to an inadequate intake of pyridoxine, and which seemed to respond dramatically to administration of that compound. Response in these same patients did not follow the therapeutic use of thiamine, riboflavin, or niacin, and additional interest in this relationship was provided by the failure of such patients to excrete within one hour a normal (6 to 10 per cent) amount of an intravenously administered test dose of 50 milligrams of pure pyridoxine. Despite these findings, this clinical state is poorly differentiated from the manifestations of deficiency of other members of the B complex and its confirmation as an entity still awaits the evaluation of extended experience.

Patients with postencephalitic Parkinson's disease also show subnormal excretion of a test dose of pyridoxine[15] but if this represents a true deficiency state, the clinical response of such individuals to vitamin therapy has been disappointing.

More recently, interest in the use of pyridoxine in postradiation sickness has been stimulated by the favorable response of suitable patients to its administration on an empirical basis. Similar results have been obtained in the treatment of the nausea and vomiting of pregnancy. Detailed assays, excretion and metabolic studies have not been made in these patients so that the basis for this therapy rests upon a very unsatisfactory foundation. In addition, not only have the results not been uniformly favorable, but Hesseltine[10] has reported equally good results in hyperemesis gravidarum from the use of distilled water.

In relation to the hemopoietic function of pyridoxine observed in experimental animals, there has not yet been found a comparable clinical condition in which bone marrow stimulation could be attributed unequivocally to the use of pyridoxine. Cantor and Scorr[4] reported successful use of the pure crystalline compound in human agranulocytosis, with a prompt response in the white blood cell count as early as the second day of therapy and reaching a maximum by the tenth day. This work, likewise, has not been generally confirmed. Therapeutic use of pyridoxine in various forms of anemia, but especially in the microcytic types which resemble the experimental deficiency state in dogs, have been almost uniformly disappointing.

Even less impressive have been the results of attempts to use pyridoxine in the muscular dystrophies. Early trials made on a purely empirical basis stimulated a temporary flurry of interest, but further careful studies again yielded no positive results, so that it seems fair to state definitely on the basis of our present information that this vitamin bears no etiologic relationship to any of the naturally occurring muscular dystrophies.

Finally, it seems worth while to consider the possible relationship of pyridoxine intake to protein metabolism in human nutrition. Although little is known about it, there is reason to believe that the anabolic phase might be strongly influenced by either the abundance or lack of this vitamin which under experimental conditions has been so clearly related to amino acid metabolism. Extensive clinical nitrogen balance studies will be necessary in order to determine the existence and magnitude of such an effect.

PANTOTHENIC ACID

Existence of pantothenic acid was probably first suggested in 1901 with the isolation of "bios," a growth substance for yeast cells. Although this term is no longer used, bios is known to contain this vitamin. It was isolated in pure form in 1940 and its chemical structure was reported that same year by Williams and Major.[30] Pantothenic acid is widely distributed in nature (whence its name is derived), and its nearly universal presence in the cells of all animals, bacteria, and yeast suggests a vital metabolic function.

The pantothenic acid content of foods is shown in the accompanying table:

PANTOTHENIC ACID CONTENT OF FOODS
(MICROGRAMS PER GRAM DRY WEIGHT)

Beef liver	240
Dried brewers' yeast	200
Pork liver	196
Liver	180
Egg yolk	125
Beef heart	122
Peanut meal	120
Eggs	108
Broccoli	87
Cane molasses	70
Pork loin	68
Leg of lamb	50
Buttermilk, churned	46
Sweet potatoes	38
Lean beef	38
Beef, round	38

Skim milk	36
Squash	35
Canned salmon	28
Irish potatoes	28
Canned pumpkin	23
Whole milk	22
Tomatoes	20
Carrots	13
Spinach	10
Onions	9
Oranges	7
Bananas	4
Canned green beans	1

Early experimental work with animals was done largely in chicks and rats in both of which a deficiency syndrome could be recognized. In chicks, a severe dermatitis develops, associated with degenerative spinal cord lesions, involution of the thymus, fatty degeneration of the liver, and poor hatchability of eggs. In black rats the picture is one of graying of hair, failure of growth, anemia, leukopenia, and hemorrhage and necrosis of the adrenal glands.[19, 24] In dogs, pantothenic acid deficiency results in severe hypoglycemia, fatty degeneration of the liver, severe gastrointestinal disorders with a failure of normal digestion of protein and carbohydrate, convulsions, and death. In swine there is a failure of growth, loss of hair, excessive nasal secretion, diarrhea associated with ulcerations of the colon, and a severe neurologic disorder characterized by a spastic, ataxic gait and degenerative lesions in both sensory and motor components.[31]

The enormous variety of these deficiency manifestations is indicative of a fundamental metabolic role for this vitamin in the functional integrity of many types of tissues. It is almost a certainty, therefore, that the common denominator in all of these experimental deficiency states involves a failure of specific enzymes for which pantothenate probably serves as a prosthetic group.

Perhaps the greatest interest has centered about two special deficiency manifestations, namely, adrenal necrosis and the graying of hair. Degenerative lesions of the adrenal cortex were first reported in 1940[19, 24] and have been studied more intensively since that time.[20, 22] These investigations indicate that pantothenic acid deficiency, in some experimental animals at least, imposes a metabolic strain upon the organism which leads to increased adrenal cortical function to a degree that rapidly produces secretory exhaustion, as evidenced by the complete depletion of steroid compounds in those areas of the gland where they are usually present in large amounts. Experiments with rats have demonstrated that achromotrichia (graying of hair) and adrenal dysfunction are intimately related. Ralli and Graef[25] have shown that adrenalectomy will restore the hair color of animals which have been depigmented through pantothenate deficiency and will accelerate hair growth in all animals whether deficient or not. In a subsequent paper[26] these same workers reported that desoxycorticosterone, and to a lesser extent adrenal cortical extracts, will prevent these effects of adrenalectomy in pantothenic acid deficient rats. In addition, some further observations suggest that dehydration and salt concentration of body fluids, two functions controlled largely by the adrenal cortex, may influence melanin production and deposition. Thus an endocrine abnormality with profound metabolic consequences has been directly related to nutritional status.

The clear association of pantothenic acid with adrenal function and hair color in experimental animals has led very naturally to the belief that a similar relationship might be established for humans. Clinical observers have been interested in and alert to the possible endocrine effects of deficiency disease without, thus far, having been able to identify a state of adrenal cortical insufficiency resulting from malnutrition. Similarly, a wave of enthusiasm was established temporarily for the hair-color–restoring power of pantothenate, and reports of its successful use even appeared in the medical literature. This hope, however, was short lived, and it is now generally conceded that the natural graying of hair in humans is based upon an entirely different mechanism, the nature of which is completely unknown at the present time.

Degenerative neurologic lesions in many species of animals with pantothenate deficiency have been responsible for a reexamination of the true etiologic factors in human deficiency polyneuritis. So complete has become the association of this lesion with a lack of thiamine that all forms of neuritis are commonly treated in most clinics with oral or injected thiamine. It does not seem unreasonable, however, that other nutritional factors in the B complex may be involved in maintaining the integrity of nervous tissue. Animal experiments have provided several suggestive leads, but much careful observation and detailed quantitative vitamin studies will be necessary to establish these relationships.

Assay methods are now available for the quantitative estimation of pantothenate in biologic material, and several studies have been reported.[21, 28, 29] Using the micro-organism *L. casei* for bioassay, the daily urinary excretion of normal adults has been found to be in the range of 1.0 to 7.5 mg. with an average of 3.5 mg. Deficient individuals excrete less than normal amounts, but after test doses of 10, 20, and 100 mg., the urinary excretion pattern does not permit a sharp separation of normal from deficient subjects. Blood concentrations of normal fasting adults vary between 19 and 23 micrograms per 100 cc. approximately 44 per cent of which is in the plasma. Administration of glucose by mouth results in a 20 to 30 per cent lowering of these values.

There are two important details in the metabolism of pantothenic acid that have increased the difficulty of interpretation of much of the experimental data. The first of these is the possible, or even probable, capacity for biosynthesis of pantothenate by intestinal micro-organisms. This abundant flora may be capable of producing considerable amounts of this as well as of other vitamins and making them available through intestinal absorption for the host's metabolism. A constant source of supply such as this would provide would be limited only by nutritional conditions so extremely poor as to curtail the growth essentials of these organisms, or by artificial quantitative reduction of the intestinal bacterial count by sulfonamides or other chemotherapeutic agents. It is quite possible that the phenomenon of intestinal biosynthesis superimposed upon the unusually wide natural distribution of pantothenic acid accounts for the rare occurrence of spontaneously developing pantothenate deficiency in man.

The second complicating factor is the capacity of pantothenic acid to combine chemically as an integral part of a protein molecule. As an amino acid it may enter by peptide linkage into protein structure, in a manner that prevents its measurement by present available methods, unless protein hydrolysis precedes the assay procedure. It is now generally recognized that the concentration of free pantothenate is very low in both plant and animal tissues and its metabolic availability may depend upon its liberation from the combined form. Little is known of the relative amounts of the free and combined forms in blood, urine, and tissues of animals, and considerably more attention must be directed to this matter.

From the strictly biochemical point of view, the most interesting development in our knowledge of pantothenic acid is the demonstration by Lipmann[23] of its participation in enzymatic acetylation. In this reaction pantothenate appears to function as a coenzyme which has been named co-acetylase. The vitamin is chemically combined in the protein structure of the enzyme from which it is liberated with some difficulty. If the function of this enzyme system is to effect biologic acetylations, the detoxification of drugs and other compounds, as well as the biosynthesis of acetylcholine, acetyl phosphate, and other metabolic intermediates, then pantothenate has indeed a very important function. A recent paper by Riggs and Hegsted[27] illustrates this function. Acetylation of intraperitoneally administered para-aminobenzoic acid in rats was reduced from 70 per cent in normal controls to 37 per cent in pantothenate-deficient animals. Added pantothenate corrected this abnormality. Thus a biochemical lead has developed which may point the way toward recognition of abnormalities that lie within the sphere of clinical medicine.

BIOTIN

Recognition of a growth factor called "bios," necessary for yeast growth, dates back to 1901. It was later shown to be a group of active substances, one of which was identified by Kogl in 1936 and named by him "biotin." In 1933 Allison, Hoover, and Burk described "coenzyme R," a compound of low molecular weight necessary for the growth of certain root nodule bacteria. A third line of investigation was begun by Boas in 1927 when she described the syndrome of "egg-white injury" in rats with the subsequent identification of a widely occurring factor which would protect against this condition. This protective substance, known also as vitamin H, is now recognized as being identical with "coenzyme R" and the "bios factor" and is known officially as biotin. Thus three independent lines of investigation converged and eventually culminated in the synthesis of this important compound in 1942 by du Vigneaud.[35]

This remarkable compound is widely distributed in nature in both plant and animal tissues, but is present in especially high concentration in yeast and liver. Its most astonishing characteristic is its extremely high potency, as evidenced by the protective dose in rats of 0.1 microgram per animal per day. This fact, together with its relative abundance in natural foodstuffs, makes it seem unlikely that biotin deficiency could be of common occurrence in humans as a result of simple dietary restriction.

The nature of egg-white injury and its relation to the protective action of biotin was worked out quite completely, even before the availability of the pure crystalline compound. Largely through the work of Parsons and her group[46] and György and his co-workers[39] it is now known that a component of raw egg white, known as avidin, combines chemically with biotin to form a stable, inactive complex which is unabsorbed from the gastrointestinal tract. The feeding of raw egg white or its active constituent therefore produces biotin deficiency by combining with and carrying through the intestinal tract much of the biotin of the diet as well as that produced by intestinal micro-organisms, and the manifestations known as egg-white injury are in reality those of biotin deficiency. Avidin is a protein of molecular weight about 70,000. The pure crystalline material has an antibiotin potency approximately 15,000 times that of the original egg white from which it is prepared. Its activity is destroyed by peptic digestion, and it is not effective when administered parenterally. In fact, hydrolysis in the tissues apparently releases some biotin so that manifestations of deficiency are actually ameliorated to some extent.

Biotin deficiency in rats produces a characteristic skin lesion which resembles eczematoid dermatitis. Loss of hair is extensive, and inflammatory areas about the eyes usually make them close. The animals lose weight, develop spastic hind legs, arching of the back, and finally terminal cyanosis and death. Biotin requirements for chicks appear to be somewhat higher than for rats so that a deficiency syndrome is more easily produced, even without the addition of avidin to the diet. The first suggestion implicating biotin with clinical conditions in man was probably that of Findlay and Stern,[36] which directed attention to the similarity between egg-white injury in rats and the childhood disease known as "pink disease." Later, György[40] pointed out the similarity of this deficiency disease in rats to seborrheic dermatitis in adult humans. A wide variety of biotin deficiency manifestations in various animal species have been reported recently. These include a failure to maintain normal muscle creatine levels, failure of normal gestation with fetal death, progressive paralysis, loss of body hair, anemia, and others. In addition, the possible role of biotin in tumor growth has been the subject of several investigations. It is difficult to find a common metabolic denominator running through these diversified experiments, and elucidation of these effects must await identification of a specific biochemical role clearly attributable to this compound.

The first experimental human biotin deficiency, however, was reported by Sydenstricker in 1942.[47] Using a diet of low biotin content, supplemented with 200 Gm. of dried egg-white daily, these investigators produced a condition characterized by a fine, scaling dermatitis which developed within three to four weeks, followed about three weeks later by a maculosquamous lesion and a peculiar grayish pallor. Atrophy of the tongue, a confused, depressed mental state with hallucinations, anorexia, and evidences of coronary insufficiency also developed as a part of the picture. Blood cholesterol and bilirubin levels were increased. Response to injection of 30 to 75 micrograms of biotin was prompt and specific. The basal biotin excretion by these patients ranged from 29 to 62 micrograms per twenty-four hours and fell at the height of the deficiency to 3.5 to 7.3 micrograms. It rose again promptly after parenteral administration of biotin.

Further significant observations in humans were made by Oppel[43] who found the daily excretion in healthy adults to vary between 14 and 111 micrograms and established a satisfactory correlation with dietary intake. Especially significant was the finding that fecal excretion regularly exceeded the intake, indicating a degree of intestinal biosynthesis that usually may be expected to supply the metabolic needs for this vitamin.

Numerous other studies have corroborated these findings, in general. Gardner and associates[37] found that normal young women excreted from 29 to 167 micrograms daily, and again these levels often exceeded the intake. Denko and co-workers[34] found in normal young men an average daily excretion of 32 micrograms which constituted 73 per cent of the intake.

More recently Coryell and her associates[33] have studied the biotin content of milk during normal lactation in the human female. During mature milk production they found biotin levels in the milk ranging from 0.24 to 25.17 micrograms per twenty-four hours, accounting for 2 to 14 per cent of the biotin intake. Urinary levels accounted for 15 to 70 per cent of the intake.

In a later study Oppel[44] has produced further evidence relative to the magnitude of this biosynthesis. The difficulty of producing biotin deficiency in human subjects through the use of avidin appears to depend upon some unknown factors in addition to the probable stoechiometric combining proportions between the vitamin and its inhibitor. Some investigators[42, 46] were unable to produce a deficiency by this means, even with the use of large amounts of avidin. On the other hand, nonabsorbable sulfa drugs have been shown to be capable of nearly complete cessation of intestinal biosynthesis of biotin, resulting in a fecal excretion of only 20 micrograms daily.

Using an oral test dose of 500 mg., an increase in the daily urinary excretion of biotin amounting to 245 to 337 mg. was produced in normal human subjects. If administered with avidin, this response did not take place. Study of various pathologic states by this technic failed to reveal any consistent abnormalities, with the possible exception of seborrheic dermatitis in which a desaturated state relative to biotin appeared to exist. Therapy with this vitamin, however, failed to yield any demonstrable result.

A diligent search is being conducted by many investigators for a possible metabolic role of this compound. Thus, in experiments with the yeast cell, *Saccharomyces cerevisiae*, Winzler *et al.*[49] have shown that a biotin deficiency in the growth medium results in a marked depression of the rates of both respiration and fermentation, with a failure of normal assimilation of ammonia nitrogen by the cells. The micro-organism *L. casei* appears capable of growth on a medium lacking in biotin, provided oleic acid is present.[48]

In animal experiments, Gavin and McHenry[38] believed that they could demonstrate the production of fatty livers in rats on a B-complex-deficient diet when biotin was added. This condition was called the "biotin fatty liver" and was thought to be resistant to the lipotropic action of choline, although it appeared to respond to inositol. Several reinvestigations of this problem, however, have failed to confirm any specific fat-increasing effect of biotin, and it seems more reasonable to attribute this result to a multiple deficiency of many factors including those in the vitamin B complex.[32, 41]

Thus, it appears to be thoroughly justifiable to conclude at the present time that students of nutrition are still very much in the dark concerning both the biochemical role of biotin and the part that its deficiency may play in human disease.

INOSITOL

The nutritional significance of inositol was first realized in 1940, although the compound has been known to chemists for many decades and its presence in living tissue was demonstrated in 1850 by Scherer in Germany. Its biologic importance, like that of biotin, came from a study of the growth stimulant "bios" for yeast culture. In 1940 Wooley[64] identified this compound as a dietary essential for the mouse, a deficiency of which led to loss of hair and failure to grow. Since that time much of its biochemical behavior has been studied, deficiencies have been produced in other animals, and possible functions in human nutrition have been postulated. Despite the scope of these investigations, inositol must still be considered as a relatively unknown nutritional factor.

Its natural occurrence is closely associated with other members of the vitamin B complex and it is quite abundant in many foods of both plant and animal origin. Heart muscle of several species has been found to be the richest dietary source, with a content of about 1.5 per cent dry weight of tissue. Cereal grains, brewers' yeast, liver, and milk also contain appreciable amounts, and corn steep liquor is probably the richest commercial source. Approximately half of the inositol in most foods is in a combined form, the availability of which, for nutritional purposes, is unknown at present. In animal nutrition, it is highly probable that a considerable fraction of the daily requirement is supplied by means of intestinal biosynthesis. The daily requirements are not definitely known for any animal species, although 10 mg. per 100 Gm. of ration will cure deficiency manifestations in mice. In humans, Williams[62] has suggested that 1 Gm. daily is probably the approximate requirement, although this estimate is not based upon clinical experimental data.

The biochemical roles of inositol are concerned chiefly with two functions: first, the possible conversion of this compound into glucose, which it resembles quite closely in chemical structure, as an accessory source of energy, especially for muscle, and second, its importance as a lipotropic agent under certain conditions. The possibility that inositol might serve as a storage form of carbohydrate was suggested by its chemical structure, which is that of a cyclic hexose. Additional weight was given to this hypothesis by the finding of unusually high concentrations in the fin muscles of certain sharks[55] and in heart muscle,[63] both of which represent tissues requiring an especially constant supply of fuel. Direct evidence on this point, however, has been provided by Stetten and Stetten[61] who have shown by means of an isotope technic that the interconversion amounts to only 7 per cent under the conditions of their experiment. Thus the quantitative importance of this function would appear to be rather insignificant.

A considerable amount of evidence upon the lipotropic effect of inositol is available. In the experimental production of the so-called "biotin fatty liver" in rats, Gavin and McHenry[56] demonstrated a fat-mobilizing action of inositol that was not equaled by choline. They believed that the lipotropic effect of lipocaic could be explained by its content of inositol. Although these experiments have been repeated by other investigators and the results challenged, the action of lipocaic still appears to be explained by its content of inositol or of inositol and choline.[50, 51, 54] A possible relationship between this vitamin and both cholesterol and unsaturated fatty acids has been suggested by several investigators. Thus, Dam[53] found that inositol was effective in reducing the cholesterol content of chick muscles, and Hermann[59] reported essentially the same effect in hens. Handler[58] demonstrated an inhibitory effect upon the lipotropic action of inositol by unsaturated fatty acids, but this observation may be related to the general nutritional status of the animals rather than to any direct interrelationship between the two components, since fatty livers do not develop unless the animals are in a reasonably good nutritional state and are gaining weight (see Chapter 22).

Woolley[65] has identified a phosphatide-like compound in soybean oil which is called liposterol and which contains inositol, galactose, ethanolamine, tartaric acid, oleic acid, and some other unsaturated fatty acids. The compound is quite stable and resists autolysis, but it is probable that it occurs in tissues and has some unknown biologic significance. One function of inositol may well be to form this compound.

In human nutrition there is no known role for inositol at present. Possible functions are based upon evidence derived from animal experiments, but no human deficiency state has been recognized. Abels and his co-workers[50] demonstrated a lipotropic action in patients with gastrointestinal cancer. The suggestion that a vitamin might be involved in the deposition and mobilization of cholesterol in the tissues has stimulated interest in the use of this compound in human atherosclerosis, but there have been no investigations reported concerning this possibility. A beneficial effect of inositol has been reported[57] in the skin disease, psoriasis, which has long been considered a metabolic disorder involving a derangement of fat metabolism. These authors believe that their results demonstrate an increased need for lipotropic substances in this condition, rather than a dietary deficiency. The failure of this method of therapy to win general approval, however, provides ample evidence that the final answer to this clinical problem is not yet available.

Perhaps the greatest clinical interest that has developed in regard to inositol thus far relates to its use in various myopathic diseases as suggested by Milhorat and Bartels.[60] Following the failure of vitamin E or tocopherol therapy of progressive muscular dystrophy to win general acceptance, these authors suggested that in the gastrointestinal tract inositol forms with tocopherol a complex which is necessary for normal creatine metabolism. They believed that this disease is due to a failure of this condensation reaction and that severe cases require the administration of the complex already formed. By means of this technic they reported successful reduction in the heavy creatinuria which is characteristic of the disease, but clinical improvement was equivocal. Unfortunately there has been no corroboration of their findings and the anticipated development of this work has not been forthcoming.

VITAMIN E

Vitamin E was first identified an an "x substance," present in green leafy vegetables and some fats, which was necessary for normal fertility in rats. This work was reported in 1922 and represented the combined work of several investigators, but especially that of H. M. Evans. Since that time, numerous studies have provided some clues to the general biologic functions of this substance and have also identified definite deficiency states in several animal species. Chemical characterization of vitamin E may be credited to P. Karrer who synthesized tocopherol at almost the same time in 1938. Despite this excellent progress a deficiency of vitamin E in humans has never been recognized and none of the various uses for either the natural or synthetic vitamin that have been suggested in human cases have withstood critical evaluation.

The chemical structure corresponding to vitamin E activity is that of tocopherol, of which there are three isomers, alpha, beta, and gamma, all possessing biologic potency. The most striking characteristic of these compounds is their antioxidant activity upon which most of their biologic functions are thought to depend. It is quite possible that the naturally occurring vitamin will eventually be found to be a complex of several compounds. The tocopherols are widely distributed in nature in both plant and animal tissues, so that a dietary deficiency occurring purely on the basis of a poor food intake is quite improbable. In addition to this, there is good reason to believe that intestinal biosynthesis is quantitatively important. For these reasons, human vitamin E deficiency, if it exists, may well be found to complicate other primary pathologic processes.

In animal experiments the lack of vitamin E has been clearly recognized. In rats it leads, in the female, to stillborn young or to resorption of the fetuses early in the course of pregnancy. Degenerative changes have been noted in the corpora lutea as early as the sixteenth day of pregnancy.[69] This is a reversible process, however, since restoration of the diet to normal allows subsequent pregnancies to proceed to term. In the male, however, irreversible changes in the testes involving the seminal epithelium produce permanent sterility. These changes are accompanied by the appearance of typical castration cells in the pituitary, and effects are noted also in other endocrine organs. These consist of adrenal atrophy and thymus hypertrophy, and enlargement of the thyroid. In skeletal muscle, extensive pathologic changes occur, which have been studied by many investigators.[76] This problem has been observed most carefully in rabbits, in which a diet treated with ferric chloride to destroy the vitamin E it contains leads to the appearance of dystrophic changes which bear a striking histologic resemblance to those of human muscular dystrophy. A recent paper by Hummel and Basinski[72] reports the oxygen consumption of this dystrophic muscle to be approximately double that from normal rabbits. Addition of tocopherol to the Ringer-phosphate medium did not produce any change in either the normal or dystrophic muscle. Degenerative lesions are seen also in the central and peripheral nervous systems, resulting in a progressive process with manifestations resembling in many ways those seen in human tabes dorsalis, combined system disease of pernicious anemia and progressive spinal muscular atrophy, and leading eventually to the death of the animals.[69]

These observations led naturally to an interest in an investigation of the possibility of a similar etiologic relationship in the corresponding human diseases. For a great many years the empirical use of vitamin E preparations in cases of human sterility and habitual abortion has been widely practiced, and there have been few critical studies, probably because methods for chemical determination or assay of vitamin E have been lacking. The therapeutic trials themselves have been uniformly disappointing and it must be concluded at the present time that vitamin E bears no known relationship to human fertility.

In relation to progressive muscular dystrophy, a few critical investigations have been made. Milhorat and Bartels[74] suggested that tocopherol administered with inositol was capable of reducing the creatinuria which is characteristic of the disease. Clinical improvement in these patients was equivocal. Shank, Gilder, and Hoagland[79] were not able to demonstrate any therapeutic benefit from the use of either alpha tocopherol or wheat germ oil. Thus vitamin E has proven to be ineffective in the clinical management of patients with myopathies of various types.

While these clinical studies have been in progress, a number of investigations have yielded some information relative to the biochemical properties of the tocopherols. The antioxidant effect is now well established. Vitamin E has been shown capable of protecting vitamin A from oxidative destruction. Protection of body fat from oxidation has been demonstrated in hogs[66] by Chipault *et al.*, and a rise in butter fat production by dairy cows in response to supplements of tocopherol has been shown by Harris *et al.*[70] In chicks, vitamin E deficiency leads to an exudative diathesis, the appearance of which is accelerated by the inclusion of unsaturated fatty acids in the diet. It is the opinion of Dam[67] that this condition is due to abnormal products of oxidation of the unsaturated fatty acids which are protected from destruction by tocopherol. A pigment, ceroid, has been found regularly in the smooth and skeletal muscle of vitamin-E-deficient rats, and in the livers of animals on low-protein diets. This pigment has been studied[73, 82] and is believed to be an abnormal metabolite, possibly from fat oxidation, and its occurrence is prevented by vitamin E. The formation of acetylcholine by surviving frog brain is increased by the addition of alpha tocopherol to the medium,[77] and an anti-oxidant effect again appears to be the most likely explanation in view of the anaerobic activity of choline acetylase.

A biochemical method for determination of vitamin E levels in biologic fluids is now available[75] and has been applied to human studies, but the technic is still not completely satisfactory. Using this method, blood levels for adult men and women in good health were found to be 0.19 and 0.22 mg. per 100 cc. per cent respectively. Pregnant women at term show levels 65 per cent higher than those of nonpregnant controls.[81] Cord blood of infants at birth averages about one fifth the level of their mothers. Reasoning from the known facts in various animals, Hickman and Harris[71] estimated the needs of healthy adults for vitamin E at about 30 mg. daily, and Quaife and Harris[78] reported an average content of good diets of about 15 mg. daily.

Using chemical determinations, Darby, Cherrington, and Ruffin[68] have shown that patients with sprue have plasma tocopherol levels of 0.1 to 0.3 mg. per 100 cc., as compared to the normal of 1.06 mg. A test dose of 600 mg. administered by mouth resulted in a rise only one quarter as great in the sprue patients as in the normal subjects. These observations indicate the probability that impaired intestinal absorption rather than a poor dietary intake may explain the development of vitamin E deficiency in humans, if such a condition exists. Such a situation might be analogous to vitamin K deficiency and obstructive jaundice may be of importance to both.

A claim has been made by Shute and his co-workers[68] that vitamin E is effective in the treatment of coronary heart disease and congestive failure. The beneficial effect is thought to be on the coronary vascular system, and the result is manifested in increased exercise tolerance, diminution of anginal pain, and production of diuresis. These same authors[80] have achieved striking results in purpuras of various kinds through the administration of 200 to 300 mg. daily by mouth of vitamin E. In appraising this work, it is sufficient to say that the authors' claims have not been subjected to objective study, and they have not been corroborated by other investigators despite several published and unpublished attempts to verify them.

It is very obvious, therefore, that the sum total of our knowledge of vitamin E at the present time is woefully incomplete. Evidence from animal experiments leads to the almost inescapable conclusion that this vitamin plays some vital role in human nutrition as well. Elucidation of that function stands as a challenging problem for the future.

BIBLIOGRAPHY

PYRIDOXINE

1. Axelrod, A. E., Carter, B. B., McCoy, R. H., and Geisinger, R. Circulating antibodies in vitamin deficiency states: I., Pyridoxin, riboflavin and pantothenic acid deficiencies. *Proc. Soc. Exper. Biol. & Med.* 66:137, 1947.
2. Bellamy, W. D., Umbreit, W. W., and Gunsalus, I. C. The function of pyridoxine: Conversion of members of the vitamin B_6 Groups into codecarboxylase. *J. Biol. Chem.* 160:461, 1945.
3. Birch, T. W., György, P., and Harris, L. J. The vitamin B_2 complex. Differentiation of the antiblack-tongue and the "P.-P." factors from lactoflavin and vitamin B_6 (so-called "rat pellagra" factor). *Biochem. J.* 29:2830, 1935.
4. Cantor, M. M., and Scott, J. W. Effect of vitamin B_6 (pyridoxine) in treatment of leucopenia and granulocytopenia of toxic origin in humans. *Science* 100:545, 1944.
5. Cartwright, G. E., and Wintrobe, M. M. Studies on free erythrocyte protoporphyrin, plasma copper, and plasma iron in normal and pyridoxine-deficient swine. *J. Biol. Chem.* 172:557, 1948.

6. Follis, R. H., and Wintrobe, M. M. Comparison of effects of pyridoxine and pantothenic acid deficiencies on nervous tissues of swine. *J. Exper. Med.* 81:539, 1945.
7. Fouts, P. J., Helmer, O. M., and Lepkovsky, S. Anemia in dogs cured with crystalline factor I. *Am. J. M. Sc.* 199:163, 1940.
8. Gale, E. F. The bacterial amino acid decarboxylases. *Advances in Enzymology* 6:1, 1946.
9. Harris, S. A., and Folkers, K. Synthetic vitamin B_6. *Science* 89:347, 1939.
10. Hesseltine, H. C. Pyridoxine failure in nausea and vomiting of pregnancy. *Am. J. Obst. & Gynec.* 51:82, 1946.
11. Lepkovsky, S., and Neilsen, E. A green pigment-producing compound in urine of pyridoxine-deficient rats. *J. Biol. Chem.* 144:135, 1942.
12. Reid, J. T., Huffman, C. F., and Duncan, C. W. Poikilocytosis in dairy cattle. *Arch. Path.* 39:351, 1945.
13. Sarma, P. S., Snell, E. E., and Elvehjem, C. A. Biological assay of pyridoxal, pyridoxamine, and pyridoxine. *J. Biol. Chem.* 165:55, 1946.
14. Spies, T. D., Bean, W. B., and Ashe, W. F. Pantothenic acid in human nutrition. *J.A.M.A.* 115:523, 1940.
15. Spies, T. D., Hightower, D. P., and Hubbard, L. H. Some recent advances in vitamin therapy. *J.A.M.A.* 115:292, 1940.
16. Stoerck, H. D., Eisen, H. N., and John, H. M. Impairment of antibody response in pyridoxine-deficient rats. *J. Exper. Med.* 85:365, 1947.
17. Umbreit, W. W., Wood, W. A., and Gunsalus, I. C. Mechanism of pyridoxal phosphate function. *J. Bact.* 51:576, 1946.
18. Umbreit, W. W., Wood, W. A., and Gunsalus, I. C. The activity of pyridoxal phosphate in tryptophane formation by cell-free enzyme preparations. *J. Biol. Chem.* 165:731, 1946.

PANTOTHENIC ACID

19. Daft, F. S., Sebrell, W. H., Babcock, S. H., and Jukes, T. H. Effect of synthetic pantothenic acid on adrenal hemorrhage, atrophy and necrosis in rats. *Pub. Health Rep.* 55:1333, 1940.
20. Deane, H. W., and McKibbin, J. M. The chemical cytology of the rat's adrenal cortex in pantothenic acid deficiency. *Endocrinology* 38:385, 1946.
21. Gordon, E. S. "Pantothenic acid in human nutrition," in *The Biological Action of the Vitamins: A Symposium.* Chicago, University of Chicago Press, 1942.
22. Korenchevsky, V. Natural relative hypoplasia of organs and process of ageing. *J. Path. & Bact.* 54:13, 1942.
23. Lipmann, F., Kaplan, N., Novelli, G. D., Tuttle, L. C., and Guirard, B. M. Coenzyme for acetylation: A pantothenic acid derivative. *J. Biol. Chem.* 167:869, 1947.

24. Mills, R. C., Shaw, R. H., and Elvehjem, C. A. Curative effect of pantothenic acid on adrenal necrosis. *Proc. Soc. Exper. Biol. & Med.* 45:482, 1940.

25. Ralli, E. P., and Graef, I. Stimulating effect of adenalectomy on hair growth and melanin deposition in black rats fed diets adequate and deficient in the filtrate factors of vitamin B[1]. *Endocrinology* 32:1, 1943.

26. Ralli, E. P., and Graef, I. The effects of the synthetic and natural hormone of the adrenal cortex on melanin deposition in adrenalectomized black rats fed diets adequate and deficient in the filtrate factors of vitamin B[1]. *Endocrinology* 37:252, 1945.

27. Riggs, T. R., and Hegsted, D. M. The effect of pantothenic acid deficiency on acetylation in rats. *J. Biol. Chem.* 172:539, 1948.

28. Sarrett, H. P. The metabolism of pantothenic acid and its lactone moiety in man. *J. Biol. Chem.* 159:321, 1945.

29. Spies, T. D., Stanberry, S. R., Williams, R. J., Jukes, T. H., and Babcock, S. H. Pantothenic acid in human nutrition. *J.A.M.A.* 115:523, 1940.

30. Williams, R. J., and Major, R. T. Structure of pantothenic acid. *Science* 91:246, 1940.

31. Wintrobe, M. M., Miller, J. H., and Lisco, H. The relation of diet to the occurrence of ataxia and degeneration in the nervous system of pigs. *Bull. Johns Hopkins Hosp.* 67:377, 1940.

BIOTIN

32. Best, C. H., Lucas, C. C., Patterson, J. M., and Ridout, J. H. The influence of biotin upon the relative lipotropic effects of choline and inositol. *Biochem. J.* 40:368, 1946.

33. Coryell, M. N., Harris, M. E., Miller, S., Rutledge, M. M., Williams, H. H., and Macy, I. G. The utilization of biotin during lactation. *J. Lab. & Clin. Med.* 32:1462, 1947.

34. Denko, C. W., Grundy, W. E., Porter, J. W., Berryman, G. H., Friedemann, T. E., and Youmans, J. B. The excretion of B-complex vitamins in the urine and feces of seven normal adults. *Arch. Biochem.* 10:33, 1946.

35. du Vigneaud. The structure of biotin. *Science* 96:455, 1942.

36. Findlay, G. M., and Stern, R. O. A syndrome in the rat resembling pink disease in man. *Arch. Dis Child.* 4:1, 1929.

37. Gardner, J., Parsons, H. T., and Peterson, W. H. Human biotin metabolism on various levels of biotin intake. *Arch. Biochem.* 8:339, 1945.

38. Gavin, G., and McHenry, E. W. The effects of biotin upon fat synthesis and metabolism. *J. Biol. Chem.* 141:619, 1941.

39. György, P., and Rose, C. S. Comparative activity of vitamin H curative of egg white injury administered orally and parenterally to rats. *Proc. Soc. Exper. Biol. & Med.* 43:73, 1940.

40. György, P., Sullivan, M., and Karsner, H. T. Nutritional dermatosis in rats. *Proc. Soc. Exper. Biol. & Med.*, 37:313, 1937.
41. Handler, P. Dietary factors in the regulation of liver lipid concentration. *J. Biol. Chem.* 162:77, 1946.
42. Kaplan, I. I. One year observations of the treatment of cancer with avidin (egg white). *Am. J. M. Sc.* 207:733, 1944.
43. Oppel, T. W. The excretion of biotin in human urine. *Am. J. M. Sc.* 204:856, 1942.
44. Oppel, T. W. Studies of biotin metabolism in man. *Am. J. M. Sc.* 215:76, 1948.
45. Parsons, H. T., Lease, J. G., and Kelly, E. The interrelationship between dietary egg-white and the requirements for a protective factor in the cure of the nutritive disorder due to egg-white. *Biochem. J.* 31:424, 1937.
46. Rhoads, C. P., and Abels, J. C. The administration of egg white and avidin concentrates to patients with cancer. *J. A. M. A.* 121:1261, 1943.
47. Sydenstricker, V. P., Singal, S. A., Briggs, A. P., de Vaughn, N. M., and Isbell, H. Preliminary observations on "egg-white injury" in man and its cure with a biotin concentrate. *Science* 95:176, 1942.
48. Williams, V. R., and Feiger, E. A. Oleic acid as a growth stimulant for lactobacillus casei. *J. Biol. Chem.* 166:335, 1946.
49. Winzler, R. J., Burk, D., and du Vigneaud, V. Biotin in fermentation, respiration, growth, and nitrogen assimilation by yeast. *Arch. Biochem.* 5:25, 1943.

INOSITOL

50. Abels, J. C., Ariel, I. M., Murphy, H. T., Pack, G. T., and Rhoads, C. P. Metabolic studies in patients with cancer of the gastrointestinal tract: IX., Effects of dietary constituents upon the chemical composition of the liver, especially in patients with gastrointestinal cancer. *Ann. Int. Med.* 20:580, 1944.
51. Abels, J. C., Kupel, C. W., Pack, G. T., and Rhoads, C. P. Metabolic studies in patients with cancer of the gastrointestinal tract: XV., Lipotropic properties of inositol. *Proc. Soc. Exper. Biol. & Med.* 54:157, 1943.
52. Best, C. H., Lucas, C. C., Patterson, J. M., and Ridout, J. H., The influence of biotin upon the relative lipotropic effects of choline and inositol. *Biochem. J.* 40:368, 1946.
53. Dam, H. J. Toxicity of fractions of hog liver fatty acids to chicks fed a vitamin E deficiency diet. *Nutrition* 28:297, 1944.
54. Dragstedt, L. R. Lipotropic action of lipocaic: The effect of oral and parenteral lipocaic and inositol on the dietary fatty liver of the white rat. *Am. J. Physiol.* 147:346, 1946.
55. Fisher, H. O. L. Chemical and biological relationships between hexoses and inositols. *Harvey Lec.* 40:156, 1945.

56. Gavin, G., and McHenry, E. W. The effects of biotin upon fat synthesis and metabolism. *J. Biol. Chem.* 141:619, 1941.
57. Gross, D., and Kesten, B. M. Treatment of psoriasis with lipotropic substances derived from foodstuffs. *Arch. Dermat. & Syph.* 47:159, 1943.
58. Handler, P. Dietary factors in the regulation of liver lipid concentration. *J. Biol. Chem.* 162:77, 1946.
59. Hermann, G. R. Inositol decholesterization in old hens. *Proc. Soc. Exper. Biol. & Med.* 63:436, 1946.
60. Milhorat, A. T., and Bartels, W. E. The defect in utilization of tocopherol in progressive muscular dystrophy. *Science* 101:93, 1945.
61. Stetten, M. R., and Stetten, D. Biological conversion of inositol into glucose. *J. Biol. Chem.* 164:85, 1946.
62. Williams, R. J. The approximate vitamin requirement of human beings. *J.A.M.A.* 119:1, 1942.
63. Winter, L. B. The inositol content of the mammalian heart. *J. Physiol.* 103:27P, 1944.
64. Wooley, D. W. A new dietary essential for the mouse. *J. Biol. Chem.* 136:113, 1940.
65. Wooley, D. W. Isolation and partial determination of structure of soy bean lipositol, a new inositol-containing phospholipid. *J. Biol. Chem.* 147:581, 1943.

VITAMIN E

66. Chipault, J. R., Lundberg, W. O., and Burr, G. O. The chemical determination of tocopherols in animal fats: The stability of hog fats in relation to fatty acid composition and tocopherol counts. *Arch. Biochem.* 8:321, 1945.
67. Dam, H. Role of fats and certain other dietary components in vitamin E deficiency. *J. Mt. Sinai Hosp.* 12:1021, 1946.
68. Darby, W. J., Cherrington, M. E., and Ruffin, J. M. Plasma tocopherol levels in sprue. *Proc. Soc. Exper. Biol. & Med.* 63:310, 1946.
69. Einarson, L., and Ringsted, A. Effect of Chronic Vitamin E Deficiency in Adult Rats. New York, Oxford, 1938.
70. Harris, P. L., Swanson, W. J., and Hickman, K. C. D. Covitamin studies: 6., Effect of tocopherol supplementation on the output of vitamin A, carotene, and fat by dairy cows. *J. Nutrition* 33:411, 1947.
71. Hickman, K. C. D., and Harris, P. L. "Tocopherol inter-relationships." in *Advances in Enzymology.* New York, Interscience, 1946, p. 469.
72. Hummel, J. P., and Basinski, D. H. The invitro effect of tocopherol phosphate on the respiration of muscle from normal and dystrophic rabbits. *J. Biol. Chem.* 172:417, 1948.
73. Mason, K. E., and Emmel, A. F. Vitamin E and muscle pigment in the rat. *Anat. Record* 92:33, 1945.

74. Milhorat, A. T., and Bartels, W. E. The defect in utilization of tocopherol in progressive muscular dystrophy. *Science* 101:93, 1945.

75. Minot, A. S. The determination of tocopherol in blood serum. *J. Lab. & Clin. Med.* 29:772, 1944.

76. Morgulis, S. Nutritional Muscle Dystrophy. Paris, J. Hermann, 1938.

77. Nachmanson, D., and John, H. M. Studies on choline acetylase: Effect of amino acids on the dialyzed enzyme: Inhibition by keto acids. *J. Biol. Chem.* 158:157, 1945.

78. Quaife, M. L., and Harris, P. L. Molecular distillation as a step in the chemical determination of total and gamma tocopherols. *Indust. & Engin. Chem. (Analyt. Ed.)* 18:707, 1946.

79. Shank, R. E., Gilder, H., and Hoagland, C. L. Progressive muscular dystrophy: A clinical review of forty cases. *Arch. Neurol. & Psychiat.* 52:431, 1944.

80. Skelton, F., Shute, E., Skinner, H. G., and Waud, R. A. Antipurpuric action of a-tocopherol (vitamin E). *Science* 103:762, 1946.

81. Straumfjord, J. V., and Quaife, M. L. Vitamin E levels in maternal and fetal blood plasma. *Proc. Soc. Exper. Biol. & Med.* 61:369, 1946.

82. Victor, J., and Pappenheimer, A. M. The influence of choline, cystine and of α tocopherol upon the occurrence of ceroid pigment in dietary cirrhosis of rats. *J. Exper. Med.* 82:375, 1945.

83. Vogelsang, A., Shute, E., and Shute, W. Vitamin E in heart disease. *M. Rec.* 160:21; 91; 163; 230; 279, 1947.

Part III

THERAPY AND PREVENTION

Chapter 25

PRINCIPLES OF NUTRITION THERAPY

Norman Jolliffe

In each of the preceding chapters specific therapy was recommended for the deficiency disease under discussion. Therapeutic technics and minutiae of treatment varied somewhat from deficiency to deficiency and from author to author so that the reader may have gotten the idea that nutrition therapy is more difficult in practice than actually it is. For this reason, and in addition to furnish in a single chapter a practical guide for the modern therapy of deficiency disease, the various procedures are here summarized.

In reviewing the recommended treatments of nutritional disease, certain statements appear so frequently that they may be considered axiomatic. Among these are: “It is easier to prevent than to cure a deficiency disease.” “A satisfactory diet is the best foundation for both the prevention and treatment of deficiency disease.”

The treatment of deficiency disease may be either preventive or therapeutic.

PREVENTION OF PRIMARY NUTRITIONAL INADEQUACIES

The prevention of nutritional inadequacies is largely the responsibility of governmental agencies and public health authorities. The details of this task are provided in Chapter 30 on “Nutrition in Public Health Practice,” where it is pointed out that the prevention of malnutrition is, among other things, dependent upon intensive health education to the end that certain food habits are changed.

Physicians, as a group, probably can do more to change food habits than almost any other group of individuals.[1] Every patient, almost without exception, wants dietary advice, and he should not be given trivialities such as "Eat plenty of fresh fruits and vegetables" or "Eat what you want and take a vitamin capsule." The directions should be fairly specific and not too general, although a few patients prefer a detailed daily menu. In the words of Doctor McLester:[4] "The patient must learn the rationale of his diet and then do his own thinking and planning. He should have advice as to the general character of his food and he should be told, as a rule, how much of the several classes of food he should eat—how much milk he should drink daily, how many eggs he should eat, how many helpings of meat, how much fruit, how many helpings of green vegetables, how much cereal, and how much bread and butter. This instruction should be individual. If not given orally, it should be written or typewritten, never mimeographed or printed. When he is handed a little printed diet slip torn from a pad, the patient often concludes that either his needs are receiving but scant attention or the physician knows nothing about diet. If the patient's confidence is to be retained, he must be given dietary instructions in a form that indicates it is intended specifically for him." In the Appendix (Table D) are listed several normal dietary patterns arranged according to the basic seven food groups. All meet the National Research Council's Recommended Daily Allowances for the various nutrients. These normal dietary patterns include the following:

I. Moderate in fruits and vegetables
II. High in fruits and vegetables
III. For southern U. S. food habits
IV. For Italian American food habits
V. For Latin-American food habits
VI. A 3000 calory diet
VII. During pregnancy
VIII. During lactation
IX. For children between 3 and 6 years of age
X. For children between 7 and 11 years of age
XI. For children between 12 and 15 years of age
XII. For boys between 16 and 20 years of age

Diet I is intended for most persons, while Diet II is primarily for those who prefer an unusual abundance of fruits and vegetables or for those who have a tendency toward atonic constipation. Diets III, IV, and V are included to show how varying tastes and food habits can be accommodated in the normal basic seven dietary patterns. Diets VI—XII illustrate how the basic seven dietary pattern can be adapted to special physiologic circumstances. These diets, modified as necessary to meet the individual circumstances and without the evaluation of the nutrients, can be written or typewritten and handed to the patient by the physician as individual dietary prescriptions.

Fads and faulty dietary habits should not be allowed to go unchallenged. The person who never eats meat, drinks milk, eats breakfast, or combines protein and carbohydrate foods, the vegetarian and the raw food faddists should never go unchallenged. He is in need of education, discipline, or a verbal spanking and it is the physician's duty to sympathetically but firmly apply all three. Some patients may try sincerely to eat a satisfactory diet but fail because of business, working, or home conditions, or for other causes beyond their control. Others, in spite of pleading, cajoling, and verbal spankings will not eat a satisfactory diet because of habit, fads and fancies, lack of necessary information,* or sheer obstinacy. Others have real food allergies. When under these conditions or whenever a satisfactory diet cannot or will not be regularly consumed, practicality dictates that the physician prescribe the appropriate dietary supplement.[3] The appropriate dietary supplement varies as to circumstances. Failure to obtain citrus fruit suggests unsatisfactory intakes of ascorbic acid; a failure to drink milk suggests an unsatisfactory intake of calcium and riboflavin; a failure to eat meat, fish, fowl or eggs suggests unsatisfactory protein, iron and B-vitamin intakes; a failure to eat leafy-green or yellow vegetables and fruit suggests an unsatisfactory intake of vitamin A and of bulk-producing, water-carrying hemicellulose; a failure to eat enriched or whole grain cereals and bread suggests unsatisfactory intakes of thiamine, niacin and calories; the failure of an infant or child to use vitamin D milk suggests an unsatisfactory intake of vitamin D. The supplement must therefore be selected with some care as to the needs of the individual. A polyvitamin capsule will not supply calcium, iron, protein, or calories; nor will a mineral supplement supply protein, vitamins or calories; or a protein supplement supply minerals or vitamins. When the diet is unsatisfactory in protein, vitamins and/or minerals, the best supplement is usually a protein-mineral-vitamin mixture, flavored or plain, which can be added to water or milk in amounts sufficient to supplement the diet adequately. When the diet is unsatisfactory in a single vitamin, such as vitamin D, then supplementary amounts of that vitamin can be given. When, as is more usually the case, a multiple vitamin dietary inadequacy exists, a polyvitamin capsule containing supplementary amounts of the essential vitamins should be prescribed. Supplementary vitamin preparations are those which supply, in the recommended

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[*] The Food and Drug Administration expresses it as follows (Statement of policy of the Federal Security Agency under the Federal Food and Drug and Cosmetic Act, *Federal Register*, July 3, 1940): ". . . nor are most consumers sufficiently educated on nutritional questions to enable them to make an intelligent choice of combinations of unenriched foods on the basis of nutritional values."

daily doses, the amounts of vitamins sufficient to insure a satisfactory daily intake of these nutrients. The supplementary vitamin levels are listed in Table 32.

B-complex vitamin supplementation alone is indicated when the diet is unsatisfactory in the B vitamins but satisfactory otherwise. This practically never occurs except in subjects who do not eat whole grain or enriched bread and cereals. For those, 10 Gm. of brewers' yeast, or yeast and/or liver extracts, is the preferred supplement. Mineral supplementation is restricted, usually, to calcium, phosphorus, and iron. If the diet is unsatisfactory in iron, one of the ferrous sulphate preparations is satisfactory. Calcium-phosphorus supplementation is more difficult, in spite of the numerous preparations available. Those in tablets or capsules are generally unsatisfactory because of the number that must be taken to supply even the minimum requirements. Those in powder or effervescent granule or wafer form are more satisfactory, particularly if they can be administered on an empty stomach an hour before meals.

PREVENTION OF SECONDARY OR CONDITIONED NUTRITIONAL INADEQUACIES

The prevention of secondary or conditioned nutritional inadequacies due to illness lies almost entirely in the hands of the practicing physician. As pointed out in Chapter 1 on the "Pathogenesis of Deficiency Disease," nutritional failure may be associated with almost any disease and in many instances is promoted by the therapeutic procedures directed toward the primary illness. The part played by these two factors, intercurrent illness and therapy, in precipitating nutritional failure has just begun to be recognized. The importance of nutrition to the recovery of the patient and the speed of convalescence has been pointed up by recent studies showing the frequent nitrogen deficit of many patients subjected to surgical procedures and the so-called "toxic" destruction of protein occurring in patients with fever (Chapter 7 on "Protein Malnutrition"). Conditioning factors are especially important in patients who have had poor food habits. Often it is only the occurrence of some conditioning factor that determines whether this person or that person develops a deficiency disease.

It is obvious that reliance for preventing nutritional failure during any illness must be in food, for an adequate diet suitable to the circumstances provides essential nutrients impossible to encapsulate or provide in ampules or tablets. During ordinary illness, when no special nutrition problem is involved and the gastrointestinal tract is normal, but when eating is more of an effort and duty than a pleasure, the maintenance of good nutrition and the prevention of a nitrogen deficit pays dividends in more rapid ambulation, convalescence, and return to work. For these patients, the author prescribes a glass of skimmed milk (or if the patient is under weight, whole milk) enriched with two tablespoonfuls (30 Gm.) of a vanilla flavored powdered whole protein-carbohydrate mixture. (The high protein drink recommended on page 199 in Chapter 7 may also be used.) Each glass will provide 190 calories (275 calories if whole milk is used) and 26 Gm. of protein of high biologic value. Almost every patient will take three or four glasses of this mixture daily, giving 78 to 104 Gm. of protein to maintain nitrogen balance. Whatever other food the nurse or the family can cajole into the patient then goes into preventing a caloric deficit. This routine, along with a supplementary or a therapeutic formula polyvitamin capsule, supplies the nutritional needs for the ordinary patient without any special dietary problems, who will recover from his illness within a few days.

In the Appendix (Table D) are listed several modifications of normal diet patterns for therapeutic purposes. These diets include:

XIII. A Liquid Diet
XIV. A Liquid Diet for Tube Feeding
XV. A Soft, Low-Fiber Diet
XVI. A Bland Diet
XVII. A High-Protein Diet
XVIII. A Low-Fat Diet
XIX. A Low-Cholesterol Diet

The nutritive values of these diets, except where indicated, are satisfactory for patients with normal requirements. For patients with conditioning factors, supplementation is almost always advisable or necessary.

AMINO-ACID SUPPLEMENTATION

Several methods of meeting the needs of patients with increased amino acid requirements are available, the choice depending upon a number of factors.

If strength and the digestive tract are approximately normal, food protein of high biologic value is usually the method of choice. An additional 15 to 20 Gm. of biologically good protein can be supplied by the following: 2 glasses of milk (skimmed milk or buttermilk), 85 Gm. (3 oz.) of cottage cheese, one average portion of meat, 3 egg whites, and 43 Gm. (1½ oz.) of skimmed milk powder. It is relatively easy for the nurse or dietitian to add the egg white and skimmed milk powder to other foods that the patient is taking. By this method the addition of 45 to 60 Gm. of protein daily is often possible without meeting patient resistance.

If the digestive tract is normal but the strength or will of the patient is not sufficient for him to take this extra food, add powdered protein-carbohydrate mixture to water, skimmed or whole milk as directed for the uncomplicated patient.

Preoperatively, postoperatively, and in numerous medical conditions where the patient cannot digest or absorb protein in food, because of infection, diarrhea, and absence of proteolytic enzymes, protein hydrolysates in which 50 per cent or more of the protein is broken down to amino acids are indicated, in order to prevent protein inadequacies. The taste of protein hydrolysates is disagreeable to many patients. Most patients, however, can be induced to take them, prepared as described in Chapter 7 or if their flavor is disguised by the various methods given in the literature accompanying the commercial products. Sometimes it is advisable to give such oral preparations by stomach tube or by drip through a nasal catheter.

When the patient's disease is such as to permit inadequate or no protein ingestion, or when complete gastrointestinal rest is indicated, the parenteral route of administration is necessary. By this route 50 Gm. of protein in the form of digests or hydrolysates can be given within three hours. One, two or, rarely, even more 50 Gm. units can be given intravenously to help maintain protein nutrition.

VITAMIN SUPPLEMENTATION

Conditioning factors (Chapter 1) usually indicate a need for an increased vitamin intake. For patients able to take one of the therapeutic diets listed in the Appendix, usually one supplementary polyvitamin capsule daily is indicated as a preventive measure.

TABLE 32. SUPPLEMENTARY VITAMIN LEVELS*

Vitamin A	4000–10,000 I.U.
Vitamin D	400– 1000 I.U.
Thiamine hydrochloride	1– 3 mg.
Riboflavin	2– 3 mg.
Niacinamide	10– 50 mg.
Ascorbic acid	30– 100 mg.

* It is felt by the author that folic acid should not be included in either supplementary or therapeutic multiple vitamin preparations as many people take these preparations without medical supervision. The inclusion of folic acid would probably prevent or relieve the anemia fraction of addisonian pernicious anemia thereby delaying or preventing medical supervision and diagnosis. This delay in treatment with adequate amounts of either refined liver or vitamin B_{12} may result in a chronic or fulminating combined system disease. Experience so far with vitamin B_{12} or with refined liver extract indicates that the chronic forms of combined system disease are relatively irreversible.

When the patient's disease is such as to permit no ingestion or when complete gastrointestinal rest is advisable, parenteral administration of the vitamins along with crude liver extract is indicated. Several excellent preparations of the water-soluble vitamins are available for this purpose. They can be added to infusion fluids or can be given separately. The amounts of thiamine, riboflavin, niacinamide, and ascorbic acid, listed in Table 32 are adequate for preventive purposes when given once or twice daily, though larger doses customarily are administered. There are preparations available for intramuscular administration which combine the water soluble vitamins with crude liver. Such preparations should not be added to infusion fluids or be given intravenously. As parenteral alimentation is a temporary expedient, it is not necessary, as a rule, to give the fat-soluble vitamins A and D by parenteral injection for preventive purposes. If, however, parenteral alimentation is required for weeks or months, 100,000 units of vitamin A and 4000 units of vitamin D can be given intramuscularly at weekly intervals.

THERAPEUTIC USE OF VITAMINS

Successful treatment of vitamin deficiency diseases involves many factors other than giving vitamins. It involves careful diagnosis, for no therapy is dependable when based on slipshod diagnosis. It involves the treatment and whenever possible the elimination of conditioning factors. It involves symptomatic treatment, for a comfortable patient is of great aid to the doctor and to himself. It finally involves nutritional therapy in sufficient amounts and over a sufficient period of time to evoke maximal reversal of the nutritional lesion.

Adequate nutritional therapy does not consist in giving only the nutrients of which a deficiency is clinically manifest. It is known that most deficiency states involve multiple factors, and that deficiency diseases clinically evident are usually associated with additional tissue deficiencies of nutrients not yet clinically manifest. Adequate therapy of a deficiency disease, therefore, requires not only administration of sufficient amounts of the specific nutrient over a long enough time to obtain maximum reversal of the manifest lesion but also the restoration of tissue normality in all the essential nutrients. This can be accomplished best by the judicious combination of diet, the whole natural B complex, the essential vitamins, and specific therapy.

The best diet possible under the conditions is essential. This means a full, nutritious, high-protein diet administered in amounts sufficient to meet the energy requirements of the patient. One of the modifications of normal diets for therapeutic purposes listed in the Appendix will satisfy the dietary needs of most patients. Food is essential for it contains, along with the known nutrients, unknown factors which cannot yet be obtained otherwise. In addition, the prescription of the proper diet is a means of educating the patients to its value, in the hope that they will continue it when other therapy is discontinued.

The whole vitamin B complex is given as discussed in the paragraph on prevention of nutrient deficiencies in the presence of conditioning factors. Here, however, larger amounts are given, three to five times those used for prevention.

Therapeutic dosages of the essential vitamins are also given, as almost every manifest deficiency disease is associated with multiple tissue deficiency of these vitamins. A practical formula available through several pharmaceutical houses is one containing about the following composition: vitamin A, 25,000 units; vitamin D, 1000 units; thiamine, 5 mg.; riboflavin, 5 mg.; niacinamide, 150 mg.; and ascorbic acid, 150 mg. The administration of this formula twice daily for a week or ten days is effective in helping to restore normal tissue levels of these essential vitamins. After this period, administration once a day is usually sufficient.

To this basic therapy of diet, vitamin B complex, and essential vitamins are added extra amounts of the specific nutrients indicated by the manifest deficiency diseases. Thus, if there are lesions of vitamin A deficiency, 50,000 to 150,000 I. U. of vitamin A are given. Similarly, for their specific lesions, 10 to 20 mg. or even 100 mg. of thiamine, 5 to 15 mg. of riboflavin, 100 to 1000 mg. of niacinamide, 100 to 1000 mg. of ascorbic acid and 10 to 20 mg. of folic acid are administered. In acute deficiencies this treatment may be required for only days or at most weeks; for chronic deficiencies treatment may be required for much longer periods.

BIBLIOGRAPHY

1. Jolliffe, N. "Nutrition and the deficiency diseases" in *Preventive Medicine in Modern Practice.* New York, Hoeber, 1942.
2. Jolliffe, N. Conditioned malnutrition. *J.A.M.A.* 122:299, 1943.
3. Jolliffe, N. The preventive and therapeutic use of vitamins. *J.A.M.A.* 129:613, 1945.
4. McLester, J. S. "The normal diet" in Wohl, M. G. *Dietotherapy, Clinical Application of Modern Nutrition.* Philadelphia, Saunders, 1945.

Chapter 26

DIETOTHERAPY

Michael G. Wohl

ALTHOUGH the average physician realizes that modern scientific nutrition is a useful branch of medicine, he often knows too little of the details of the fundamental principles of nutrition to apply them. This manifests itself in the practice of prescribing a "reducing diet," a "gallbladder diet," an "ulcer diet," and so on, and of leaving the details to the hospital dietitian. The same physician would scarcely leave his pharmacotherapeutic problems to the druggist; certainly he would not order "a course of digitalis" for a patient with cardiac failure.

There are two reasons for this casual or diffident attitude toward nutrition. The first is that the medical schools have been slow to incorporate the science of nutrition within the medical discipline. The second is that the enormous literature of nutrition has been largely scattered in a diversity of technical journals not readily available to the general practitioner.

Before discussing diet therapy in relation to specific diseases, it will be useful to consider some general principles of nutritional therapy. Three such principles should be borne constantly in mind: (1) nutritional deficiencies concomitant with disease must be looked for and cleared up; (2) the therapeutic diet is a modified normal diet; and (3) the therapeutic diet must be psychologically acceptable to the patient.

CONDITIONED DEFICIENCIES

A patient may be successfully treated for an organic disease like diabetes mellitus, colitis, peptic ulcer, or anemia and yet continue to exhibit some vague nonspecific sign or symptom. The underlying reason frequently is an undiagnosed nutritional deficiency concomitant with or conditioned by the organic disease. It is often overlooked that during illness there may occur a catabolic loss of nitrogen, or interference with the utilization or absorption of one or several nutrient factors, or perhaps an imbalance in the interrelationship between nutrients. This leads to conditioned nutritional deficiency. Unless it is corrected the patient may remain chronically ill despite the fact that the underlying disease has been brought under control. It follows that conditioned nutritional deficiencies often retard convalescence and interfere with recovery from an independent disease. The conditioning factors likely to be associated with nutritional deficiency have been tabulated in Table 7, p. 124.

Therapeutic Diet

Insofar as possible, every special diet should be patterned after a normal diet, consist of natural foods, and maintain the patient in nutritional homeostasis. Indeed, the therapeutic diet is merely a normal diet, quantitatively and qualitatively modified to combat a specific physiopathologic process.

Psychologic Factors

In prescribing a special diet the physician must consider the patient's emotional and environmental status. The patient should find the diet psychologically acceptable and be able to follow it at home. The physician should consider, further, that anyone subjected for any length of time to a special diet is likely to undergo certain psychic trauma; since he is not like other people in this respect, he is not like them in others and cannot compete with them. If the patient is a child, he is likely to become a problem child. Children should therefore be taken off a special diet as soon as possible. What is more, the special diet, particularly for a child, should always be arranged so as to be as inconspicuous as circumstances will permit.

Overeating is another psychologic factor encountered in diet therapy.[3, 19, 23] Overeating is the weapon with which patients often meet traumatic experience, failure, and disappointment. For such patients, especially if they are children, keeping to a diet is hard. The physician whose patient fails to keep to a prescribed diet is sometimes inclined to become disgusted with him and assume a punitive attitude. This is both irrelevant and ineffective. It is the physician's part to discover what makes keeping the diet difficult. Knowing the patient's problems will help the physician encourage him to keep to his diet.

FEBRILE DISEASES

Nutritional requirements in febrile diseases depend on three metabolic changes that occur during fever: (1) heightened metabolism; (2) catabolic loss of nitrogen; (3) disturbed water balance. From studies conducted by Du Bois and his associates it is known that a rise in temperature of 1° C. heightens basal metabolism by about 13 per cent. If the patient is "toxic," another 10 per cent should be added; if he is restless, from 10 to 30 per cent more may be added according to the degree of restlessness and muscular activity. In planning the patient's diet, therefore, it is important to remember that his caloric requirement is 30 to 50 per cent or more above that of the nonfebrile patient, and if his caloric intake is inadequate he will consume his own tissues.

Difficulty arises, however, from the fact that a high caloric diet is not well tolerated by the febrile patient. With such a diet he tends to become nauseated, depressed, and frequently suffers from "gas." Much, then, must depend on nursing. Perhaps the most practical course is to cater to the patient's likes and dislikes in food and employ skilful culinary strategy to insure as abundant an intake of food as possible.

In febrile diseases more nitrogen is usually excreted in the urine than can be taken into the body, even when more protein is consumed than the patient normally requires. This negative nitrogen balance is due to the so-called "toxic" destruction of protein, the degree of which depends more on the severity of the infection than on the height of the fever. In some infectious diseases the loss of body protein may run as high as 500 Gm. a day and it is doubtful whether all febrile patients can be maintained in nitrogen equilibrium. Shaefer and Coleman[20] have shown in typhoid however, that if during the height of fever the caloric intake exceeds the theoretical caloric requirement by 50 to 110 per cent and the protein intake is liberal (from 160 to 200 Gm. a day), the patient can be brought into nitrogen equilibrium and his weight maintained. As the febrile patient's metabolism is increased the glycogen in his liver and other depots tends to become depleted. Sufficient carbohydrate in the diet makes it unnecessary for the protein to be used for fuel. An adequate supply of carbohydrate will also prevent the ketosis that results from the burning of the patient's own body fat.

In brief, the diet of the patient in fever should contain carbohydrate equal to one-fourth or one-half his daily caloric need; that is, from 220 to 420 Gm.

Since during fever the metabolism of fat is not changed, the inclusion of fat in the diet may help reduce the caloric deficits. Fat may be given in the form of butter, cream, or eggs.

Febrile patients may have to be given either synthetic vitamins or vitamins in such natural supplementary foods as brewers' yeast or rice bran extracts. This necessity may arise from the following causes: (1) The foods allowed to such patients frequently lack some of the essential vitamins; (2) In acute and chronic fevers the need for thiamine chloride and vitamin C is increased; (3) In patients treated with sulfonamides by mouth, there is increased excretion of vitamin C and inhibition of the synthesis by intestinal bacteria of certain vitamins, especially some of the B complex factors and vitamin K.

During a fever a negative water balance may develop and cause a greatly reduced and concentrated output of urine. In almost all cases of fever, for example, the excretion of chlorides is diminished. It is obvious that patients with prolonged fever require ample fluids, from 3000 to 3500 cc. daily.

Febrile patients suffering from salt depletion should receive from 15 to 20 Gm. of sodium chloride daily unless edema complicates the situation.

Acute Febrile Diseases

In the dietary management in the treatment of brief fevers such as acute upper respiratory infections, maintaining the fluid intake plus whatever food the patient desires is often all that is required. If the fever is more serious, as in pneumonia, or of more than a few days' duration, a liquid diet (Appendix Table D) should be provided in which milk and fruit juices are the mainstays and soft-boiled eggs, cooked cereals, and custards the supplementary foods. As convalescence progresses, more and more solid food is added. It has been stressed recently that through the prevention of the development of hypoproteinemia and anemia the course of pneumonia may be made less precarious and convalescence hastened.

Chronic Febrile Diseases

In febrile illness lasting for more than seven days the caloric requirement is large. As Shaefer and Coleman[20] have demonstrated, typhoid patients can be brought into nitrogen balance with a diet providing from 3500 to 5000 calories a day, from 70 to 90 Gm. of protein, and enough carbohydrate to make up the greater part of the energy intake and maintain weight. With such a diet mortality is lessened, the patient shows marked improvement in well-being, loss of weight is greatly curtailed, and convalescence is accelerated.

During the first few days of a long febrile illness a liquid diet is usually given. As the patient slowly recovers he is given first a soft diet and then a general diet without roughage.

TUBERCULOSIS

The relationship between nutrition and chronic febrile disease can best be appreciated through a consideration of certain nutritional aspects of tuberculosis. It has long been assumed that malnutrition predisposes to tuberculosis; and the grave increase in the incidence and severity of tuberculosis and the appalling rise in the tuberculosis death rate in Europe after both World Wars strongly support this supposition. The newer knowledge of nutrition indicates, however, that among other major nutritional factors attendant upon malnutrition and involved in reduced resistance to tuberculosis are protein inadequacy and possibly deficiencies in vitamins A and C. Indeed, the cod-liver oil and tomato juice "cocktail," rich in vitamins A and C has been suggested as a prophylactic against the development of extrapulmonary tuberculosis in the phthisical patient.

The adverse effect of protein deficiency on resistance to tuberculosis is evident in the following facts cited by Long:[11]

1. During World War I, when the significant dietary shortages were in proteins and fats, the tuberculosis death rate in Europe rose sharply. The inference is that, in many instances, a diet poor in protein and fat provides insufficient nutrients to prevent tuberculosis activity in patients who would otherwise be safe with normal diets.
2. The tuberculosis death rate in Denmark rose early in the First World War but dropped sharply in 1918, presumably because the stringent blockade of 1917 obliged the Danes to consume their own abundant supplies of meat, milk, and butter. Long refers to Faber's conclusion that the increase in the tuberculosis death rate was closely related to the shortages of meat and fish; that the original rise in the tuberculosis death rate was the result of protein deficiency.

In addition to suffering from protein deficiency, the tuberculosis patient may suffer from deficiencies of ascorbic acid, vitamin A, and, in the advanced stages of the disease, calcium. The deficiencies in ascorbic acid and Vitamin A appear to be in proportion to the extent of the tuberculous involvement.

It is interesting to note also that Getz and Koerner[5, 6] have shown that vitamin A deficiency can be correlated with the incidence of tuberculosis.

DIETARY MANAGEMENT

A proper, well-balanced diet, supplementing the medical and surgical measures, is always indicated for the tuberculous patient.

Although he should be well nourished he should not become fat. The daily diet should provide from 2500 to 3000 calories. It should be rich in protein, moderate in fat, and low in carbohydrate, and be supplemented with vitamins A and C and with calcium.

The following food items are frequently used in the dietary treatment of tuberculosis: milk and eggs in abundance; orange juice and tomato juice; cooked whole-grain cereals and bread; leafy vegetables; meat, especially liver and other visceral meats; fish; and dairy products other than milk, as butter fat and cheese. Tuberculous patients can tolerate animal fats better than vegetable fats. However, olive oil is preferable to other oils for the tuberculous patient's salad dressing.

GASTROINTESTINAL DISEASES*

Malfunction of the gastrointestinal tract is prone to influence absorption and utilization of nutrients and deprive the body of essential food factors. In the treatment of such malfunction, therefore, various dietary adjustments, depending on the nature of the physiologic disturbance, become necessary to insure nutritional homeostasis and the replacement of tissue lost through disease. This is not always easy. It may be difficult, for example, to arrange for an adequate intake of protein or fat or carbohydrate, or of vitamins or minerals. Modifications may be necessary in the frequency of feedings, or in the quantity or the texture, or simply in the appearance of the food served.

Such transient conditions as acute gastroenteritis do not, of course, present a serious problem. Adequate therapy for such conditions usually consists of gastrointestinal rest and restoration of the fluid and electrolyte loss. The importance of restoring potassium stores has only recently been recognized. In chronic gastrointestinal disease maintenance of good nutrition may mean the difference between recovery and invalidism.

In an attempt to organize and simplify a working conception of diet therapy, four basic plans are outlined here in Table 33, covering the most important gastrointestinal diseases. Although the physician may use the table as a guide in preparing diets for patients with gastrointestinal diseases, he should remember that because of the many manifestations of gastrointestinal disorders, adjustments and variations are required in individual cases.

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* I am indebted to Dr. N. G. Schneeberg for assistance in writing this subsection.

TABLE 33. SIMPLIFIED DIET SCHEME FOR GASTROINTESTINAL DISEASES

Disease	Diet	Frequency	Carbohydrate	Protein	Fat	Calories	Vitamin concentrates
I. Functional g.i. disorders (nervous indigestion, flatulent dyspepsia, intestinal CHO dyspepsia)	Bland	T.I.D. or frequent small	Normal or somewhat reduced	Normal, may be finely divided	Normal	Normal	Not required
Gastritis, chronic	Bland	Frequent small	Normal or somewhat reduced	Chopped, sieved, no roughage	Normal or reduced	Normal	Required
Hyperchlorhydria	Bland	Frequent small	Normal or somewhat reduced	Chopped, sieved, no roughage	High	Normal	Required
Peptic ulcer	Omit gastric secretagogues	Frequent small	Normal or somewhat reduced	As above	Easily digested	Normal	Required
Spastic colon (mucous colitis) Spastic constipation	Bland, low residue	T.I.D.	Normal	Normal, may be finely divided	Normal	Normal	Required
II. Gastritis, acute Hematemesis Postoperative Gastroenterostomy	Bland	Frequent small	Normal or reduced	Normal, finely divided	Normal or reduced	Normal or reduced	Required
III. Diarrhea	Bland, low residue	Frequent	Normal	High	Low	High	Required
Ulcerative colitis	"	"	"	"	"	"	"
Sprue (idiopathic steatorrhea)	"	"	Reduced, ripe fruit, bananas	"	Very low	"	"
IV. Atonic constipation	Bulky high residue	T.I.D.	Normal	Normal	Normal	Normal	Not required

Modified from DUNLOP, D. M. The dietetic treatment of gastro-intestinal disease. *Edinburgh M. J.* 48:731, 1941.

Group I plan: The diet is one of low residue (Appendix Table D), smooth, bland, and intended to provide small but frequent feedings. The carbohydrate is kept normal in quantity or slightly below normal; the protein is kept adequate in quantity and is prepared in finely divided form; the fat is provided in the most digestible form (butter or margarine, eggs, and cream).

Group II plan: The diet (Appendix Table D) is designed for acute and subacute conditions and is planned to follow an initial period of five or ten days of liquid feedings.

Group III plan: The diet is designed for use in chronic diarrheal diseases (Appendix Table D). It is similar to that in the Group I plan but is more emphatically a low-residue diet. The protein intake provided is high, the fat intake low.

Group IV plan: This high-residue diet (Appendix Table D) is designed for cases of atonic constipation only.

Peptic Ulcer

Although many diets have been devised for the treatment of gastric and duodenal ulcer, milk remains the prime therapeutic food in the initial stages of either kind of ulcer. Peptic ulcer is associated with hypermotility, hyperperistalsis, hypertonicity, and hypersecretion. Milk and cream possess high acid-neutralizing power in the stomach; in the duodenum they stimulate mechanisms that bring about gastric motor and secretory inhibition. Despite evidence that ulcer pain may not parallel the degree of hyperchlorhydria and that it is impossible to neutralize gastric acid completely for twenty-four hours without using a continuous intragastric drip of milk or colloidal aluminum hydroxide, the generally accepted aim of therapy in peptic ulcer is the neutralization of the free hydrochloric acid in the stomach with a minimum of motor activity.

The ulcer diet must supply sufficient calories, eliminate all foods having strong acid-stimulating properties (as meat and fish extractives, salted or pickled foods, condiments, charged waters, iced drinks, coffee, and alcohol), be moderately rich in fat (to inhibit gastric overactivity), and supply adequate protein, vitamins, and minerals. Although patients with uncomplicated peptic ulcer have rarely shown significant weight loss or gross malnutrition, they have shown deficiencies in total serum protein, especially as this is reflected in the albumin fraction, and in vitamin C levels.

The trend in ulcer therapy is toward more liberal diets, with emphasis on proteins and vitamins. The use of protein hydrolysates has been advocated, for example, as a means of supplying the necessary protein in a bland and easily assimilable form which at the same time has antiacid properties. Recently Co Tui *et al.* gave a group of ulcer patients bi-hourly feedings of an enzymatic protein hydrolysate and Dextrimaltose.[18] In twenty-four hours these feedings supplied from 30 to 48 mg. of nitrogen and from 40 to 50 calories per Kg. of body weight. The treatment was efficacious in ameliorating ulcer symptoms, favored healing of the ulcer, and restored strength and body weight. Many patients so dislike protein hydrolysates that in practice they are not useful. To supplement the diet with protein, powdered skim milk or an available protein concentrate may be used.

Until they are able to tolerate a well-balanced diet, ulcer patients should usually be given vitamin concentrates, especially the water-soluble vitamin C and thiamine chloride. This will offset the vitamin deficit in the diet and the interference with vitamin utilization caused by alkali therapy.

For the rest, the importance of psychotherapy for the ulcer patient, of rest and relaxation, administration of sedatives and antispasmodics, and abstinence from tobacco, cannot be too highly emphasized.

The following diet recommended for peptic ulcer is a guide, not a rigid formula.

PEPTIC ULCER DIET*

First Seven to Ten Days

1. The patient should take 113 Gm. (4 oz.) of milk-cream mixture every hour, 8 A.M. to 9 P.M. Mixture consists of 700 ml. (1½ pints) of milk, 230 ml. (½ pint) of table cream, and 30 ml. (2 tablespoonfuls) of lactose. The ambulatory patient can carry this about with him in a quart thermos bottle. Before it is drunk, each feeding should be allowed to approach room temperature. No other food or drink but water is to be taken. If pain breaks the patient's rest or keeps him from sleep, night feedings are in order.
2. By way of adjuvant therapy, an antispasmodic or sedative may be used.
3. If symptoms do not abate, 8 Gm. (2 dr.) of colloidal aluminum hydroxide fifteen minutes before each feeding from 8:45 A.M. to 8:45 P.M. should prove helpful.
4. In intractable cases, continuous intragastric milk drip at night, or even day and night through a Levin tube, may control symptoms. If the drip rate is 30 drops a minute, day and night, 2880 cc. of milk will be supplied, equal to 100 Gm. of protein and 1980 calories.

When Clinical Improvement Is Observed

A three-meal-a-day regimen is now in order, consisting of cooked cereals, rice boiled to a mushy consistency, cream soups, baked and mashed potatoes, puréed green and yellow vegetables (as green beans, squash, and carrots), and applesauce. Interval and bedtime feedings should consist of milk and cream with toast, crackers, or zwieback.

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* After Bockus.[2]

When All Symptoms Disappear

Add to the diet tender boiled, broiled, and roasted meats; lean fish and poultry; puréed, strained, sieved, and chopped vegetables; junkets and custards; tapioca, gelatin, and cornstarch puddings; and baked apple. Interval feedings are continued.

When Full Diet May Be Resumed

Fried, greasy, coarse, irritating, and highly seasoned foods must be avoided; no condiments, salted or pickled foods, meat, broths or meat extracts, alcohol or coffee. Interval feedings may be necessary for years, even for life.

Hematemesis and Melena

In 1935 Meulengracht[12] presented evidence that feeding a liberal puréed diet to patients with bleeding peptic ulcer reduced mortality and morbidity among them and was superior to the classic treatment of parenteral feeding, morphine, and no food by mouth. Many authorities agree that when shock, nausea, and vomiting do not interfere, the Meulengracht method is to be preferred. Some, however, still favor the starvation treatment. Gray,[7] for example, prefers the system of hourly milk and cream feedings throughout the day and bi-hourly feedings at night. He suggests that the Meulengracht diet increases the vigor and amplitude of gastric contractions and is likely to stimulate the flow of acid gastric juice.

Disease of the Small Intestine

The functional efficiency of the small intestine depends ultimately on the nutrition of the whole organism. It has been demonstrated experimentally in monkeys that a deficient diet causes failure to gain weight, listlessness, and chronic diarrhea, and that these symptoms are associated with a severe noninflammatory degeneration of the small intestine. A strikingly similar syndrome, with similar pathologic small-intestine degeneration, has been observed in African laborers subsisting on a poor diet. It has also been demonstrated that the absorptive capacity and the motor function of the small bowel are reduced to below normal by vitamin B deficiency. Both a flat oral glucose-tolerance curve and a disturbance of the normal small-intestine X-ray pattern have been observed in human beings with vitamin B deficiency.

Dysfunction of the small intestine and the reduced absorptive capacity that follows may, however, lead to a deficiency state. It may therefore be difficult to decide whether intestinal disease is the primary disorder and deficiency disease the secondary, or vice versa. In any case, treatment obviously depends on etiology. If disease of the small intestine seems to be the ultimate cause, the primary therapy must deal with that disease. If, however, a deficiency state has caused intestinal dysfunction, the nutritional disorder must be corrected. Here the diet should be rich in protein, vitamins, minerals, and calories, and should be reinforced with vitamin concentrates.

Disease of the Colon

The diet therapy to be employed in chronic diarrhea depends on the causes and duration of the symptoms and on the patient's clinical status. Severe acute diarrhea with dehydration calls for the vigorous replacement, usually through parenteral feeding, of losses sustained in fluid, electrolytes, protein, vitamins, and minerals. During the acute stages of the dysenteries a large fluid intake is required. Water, sweetened tea, rice water, other gruels, albumin water, and fruit juices (if tolerated) are the obvious sources for this. Progression to a soft, smooth, nonirritating, low-residue diet, and from that diet to a normal one, depends, of course, on the degree of improvement the patient shows.

Nutrition is an important factor in chronic diarrhea, which may lead to dehydration and loss of protein, vitamins, and minerals. The diet for patients with chronic colitis should therefore be bland, smooth, low in residue, rich in protein and calories, and low in fat. It should provide at least 120 Gm. of protein a day. If finely divided meat, fish, and poultry, and eggs, milk, and cream are not tolerated, the protein intake must be insured through the use of albumin, gelatin, and protein hydrolysates. These last may prove particularly useful in supplying protein that can be readily absorbed with a minimum of gastric and intestinal stress.

It should be borne in mind that patients with chronic diarrhea may develop allergy to certain foods commonly prescribed for them, such as milk, eggs, and cheese. If the offending food is not eliminated from the diet the pathologic changes in the bowel may become aggravated.

Foods with a low residue include meats, gelatine, fish, boiled eggs, rice, and gruels.

Foods with a nonirritating low residue include puréed cooked vegetables, stewed fruits, fruit juices, noodles, bread, and macaroni.

Ulcerative Colitis

The principle of dietary treatment of ulcerative colitis is to maintain the patient in good nutrition while sparing the colon. These objectives are frequently difficult to attain with the foods ordinarily recommended for patients with chronic diarrhea. In this complicated situation the procedure of choice is that recommended by Machella; namely, the use of a solution of a mixture of a protein hydrolysate and carbohydrate.[11a] This form of alimentation is of value for the following reasons: (1) A high caloric intake is possible; (2) The calories are supplied in liquid form, the residue being negligible; (3) An adequate fluid intake is insured; (4) A more than adequate protein intake is automatically assured, so that a positive nitrogen balance can easily be attained; (5) The protein, being hydrolyzed, is in a readily absorbable form; (6) Little or no fat is present and the caloric deficiency due to its absence is made up by a carbohydrate such as Dextrimaltose; (7) The material is nonantigenic, so that the danger of food sensitivity is circumvented; and (8) The mixture is easily prepared and administered.

PLAN OF ADMINISTRATION

1. AVERAGE CASE:
   a. *Material:* A mixture of equal parts of a protein hydrolysate and a carbohydrate such as Dextrimaltose.
   b. *Amount:* The amount to be administered is calculated on the basis of 40 calories per Kg. of pre-illness weight. This usually amounts to 450 to 900 Gm. of the mixture.
   c. *Solution:* The measured amount is completely dissolved in enough boiling water to give a 15 to 25 per cent solution. The solution is clear when prepared and should remain so. It can be stored in milk bottles in the refrigerator. Any cloudiness developing in it indicates that bacterial growth has occurred and that it should not be administered to the patient.
   d. *Volume per feeding:* 200 to 400 cc.
   e. *Frequency of feedings:* Every two hours from 6 A.M. to 10 P.M.

2. COMPLICATIONS OF SUCH ALIMENTATION
   a. If nausea, epigastric fullness, and vomiting occur the solution is either contaminated with bacteria or is too concentrated and must be diluted. Concentrated solutions tend to remain in the stomach until they are diluted.
   b. If flatulence is complained of and is attributed to the solution, bacterial contamination should be suspected.
   c. If the diarrhea persists or increases, apparently as a result of the administered material, a "medical ileostomy" can be performed by means of a Miller-Abbott tube. Small-intestine content is prevented from entering the diseased colon by application of constant suction. The use of this technic for a period of ten to fourteen days may allow sufficient rest to

the colon to permit subsequent administration of the solution without excessive diarrhea.

3. Duration of Administration

The administration of the solution is continued for a period of three to six weeks or until clinical and sigmoidoscopic evidence of subsidence of inflammation is obtained, after which a high-caloric, low-residue diet can be cautiously instituted.

Almy,[1] however, recently fed 12 patients having ulcerative colitis large quantities of protein hydrolysates plus Dextrimaltose orally and found that only 30 per cent showed rapid gain in weight and progressive improvement; the rest showed no effect.

If sulfonamides are administered, particularly sulfasuxidine and sulfaguanidine, the synthesis of vitamins B and K by bacterial action is interfered with and supplements of these vitamins must be supplied.

Constipation

Spastic and atonic constipation clearly call for diet therapy. Spastic constipation responds best to a moderately bland low-residue diet from which irritating foods like bran, raw fruits, and raw vegetables have been eliminated. The diet for atonic constipation should supply bulk and fiber. It should include whole grain bread; vegetables such as celery, lettuce, cabbage, string beans, cauliflower, carrots, beets, and peas; fruits such as prunes, apricots, apples, figs, dates, and raisins; nuts; fish, meat, and poultry; and milk, eggs, and cream. Mineral oil is not recommended, for it interferes with the absorption of fat-soluble vitamins, calcium, and phosphorus.

The hulls of psyllium seeds, agar, bassorin, karaya, and other mucilaginous vegetable substances that absorb and retain fluids, however, render the stool pultaceous and impossible to condense into hard masses and are therefore recommended.

The deleterious effects of indiscriminate use of laxatives and purgatives must be taught the constipated patient; it is equally advisable to inform him of the fallacy of the classic conception of "autointoxication."

HEPATIC DISEASE

The modern treatment of hepatic disease is based on application of the newer knowledge of the nutrients involved in the protection of the liver against toxic agents and on recognition of the intrinsic nutritional aberrations caused by such disease.

CARBOHYDRATE

A number of hepatotoxic agents—alcohol, arsenic, chloroform, and morphine (in deep narcosis)—deplete the glycogen stores of the liver. This raises the lipid content, rendering the liver more vulnerable to toxic agents. Since glycogen displaces fat in the liver, a diet rich in carbohydrate will support and protect hepatic function, as will glucose administered intravenously. Carbohydrate, by maintaining hepatic glycogen stores, prevents the overproduction of ketone bodies and prevents the wasting of protein as fuel.

Patients with hepatic disease should receive 350 to 400 Gm. of carbohydrate a day. Good sources are sugar, honey, hard candy, jams, jellies, marmalades, apple butter, white bread, biscuits, crackers, refined cereals, tapioca, rice, potatoes, fruit juices, preserved fruits, and marshmallows.

In acute hepatic damage the patient often vomits, refuses food, or lapses into coma. When this obtains, it is advisable to administer daily 3000 to 4000 cc. of 5 to 10 per cent glucose solution intravenously. When the patient is again able to take liquids and food by mouth there is no further advantage in continuing the intravenous feedings, for, as Althausen has shown, oral and intravenous administrations of glucose result in about the same deposition of glycogen in the liver.

PROTEIN

Carbohydrate alone will not give the liver maximum protection: protein of proper quality in sufficient quantity is also needed.

The importance of the quality and quantity of protein in the treatment of liver disease has only recently been realized. Ravdin and his associates[16, 17] were the first to demonstrate it, and Miller, Ross, and Whipple[13] have confirmed their conclusions. These investigators have shown that in the presence of a high fat and a low protein content in the hepatic cell not even a high level of glycogen will prevent hepatic injury, but large quantities of the right kind of protein will. Even in the presence of large quantities of fat, for example, the proper kind of protein in the proper amount will prevent the toxic action of chloroform on the liver.

Protein is also essential for the repair of the hepatic cells and the formation of cholic acid and other bile acids. Elman and Heifetz[4] have furnished corollary evidence that protein deficiency impairs liver function. By dietary means they induced hypoalbuminemia in dogs. As the albumin fraction of the blood plasma fell to about half its original value, the protein content of the liver also decreased and vacuolation of the hepatic parenchyma developed together with impairment of liver function.

Recent experimental work indicates that hepatic injury associated with a diffuse periportal fibrosis (cirrhosis) and consisting of fatty infiltration or focal or diffuse necrosis results from reducing the protein intake and withholding the entire vitamin B complex.

For patients with hepatic disease the recommended daily protein ration is 110 to 135 Gm. The best protein is derived from milk, cottage cheese, egg whites, polished rice, dried yeast, soy bean meal, lean meats, and fish. Protein concentrates and skimmed milk powder are useful for increasing the protein intake.

The hypoproteinemia and hypoalbuminemia generally associated with cirrhosis of the liver, although perhaps attributable to many other conditions, are most probably caused by the inability of the diseased liver to synthesize protein at a rate sufficient for metabolic effectiveness. This is suggested by the diminished synthesis of fibrinogen, prothrombin, and albumin, all normally produced in the liver. As the serum albumin diminishes a corresponding change in oncotic pressure takes place, whether ascites is present or not, and a negative nitrogen balance develops. It is difficult at best to raise the albumin level of the blood. In cirrhosis of the liver, protein-rich diets as well as oral or intravenous administration of amino acids (as protein hydrolysate) do not significantly alter the level of serum protein, although clinical improvement may be noted.

Furthermore, the administration of plasma, even in great quantities, produces no more than minimal clinical effects and only limited diuresis. Thorn *et al.*[21] as well as Hoagland and his associates[8] advise the administration of salt-poor human albumin in daily doses equivalent to 10 liters of plasma (from 50 to 100 Gm.). They have reported striking rises in serum albumin levels as a result of such therapy. The subjects in some of their experiments retained about 80 per cent of the albumin injected, excreting little or none of it in the urine. Diuresis was produced, moreover, and ascites diminished. Symptomatic relief was occasionally produced through the intravenous administration, three times a week, of 20 cc. of an unrefined water-soluble extract of liver diluted to 50 cc. with isotonic sodium chloride or distilled water.[10]

Recently Hoagland and his associates[8] have questioned whether, in cirrhosis, the low level of albumin in the plasma is the determining factor in the accumulation of the ascitic fluid. They believe that an antidiuretic substance of posterior pituitary origin, excreted in the urine of patients with cirrhosis, is involved. A similar antidiuretic substance has been discovered in the urine of patients with nephrosis and premenstrual edema. In cirrhosis the antidiuretic substance is found in the urine in increasing concentration because the diseased liver cannot inactivate or alter the hormone, hence the aberrant water and electrolytic metabolism accompanying ascites.

FAT

If the intake of protein and carbohydrate is adequate, the content of fat in the liver will remain constant; for fat is not stored in the liver. But under certain experimental and clinical conditions—alcoholism, for example—the liver fat is increased and hepatic dysfunction results. Both starvation and fatty diets likewise increase the rate at which the liver is supplied with fat. Furthermore, cholesterol feedings, various toxins, and want of lipotropic factors in the diet reduce the mobilization of fat from the liver.

The daily amount of dietary fat formerly recommended for patients with hepatic disease was 50 to 70 Gm.; it is now 75 to 175 Gm. This higher fat allowance offers a number of advantages. Fat makes food more appetizing and easier to prepare, gives it greater staying quality, renders utilization of the fat-soluble vitamins possible, and, as recent work has shown, supplies unsaturated fatty acids that cannot be synthesized in the body.

There is no convincing proof that in the presence of high levels of protein and carbohydrate a moderate fat intake will lead to excessive deposition of fat in the liver.

LIPOTROPIC FACTORS (See Chapter 27, p. 561.)

It is generally held that the hepatic damage attendant upon a low-protein diet is the result of the deficiency of lipotropic factors in that kind of diet.

A lipotropic factor is one that either inhibits the deposition of fat in the liver or mobilizes fat from that organ. Cystine, inositol, lipocaic, choline, and methionine are known lipotropic factors. The last two have attracted widest experimental and clinical attention.

Though methionine has been used in the treatment of acute hepatic damage, current reports indicate that at least the oral administration of it neither ameliorates the severity nor curtails the duration of infectious hepatitis; nor will such therapy prevent relapses. Methionine is said to have been more successfully employed, however, in the prevention and treatment of liver damage caused by arsenic, carbon tetrachloride, and TNT poisoning.

The value of choline and methionine* in the treatment of chronic hepatitis, portal cirrhosis, is not certain, either. For where cirrhosis patients treated with choline or methionine have shown improvement (both clinically and as measured by liver-function tests), there has been supplementary treatment with multiple vitamins and a diet low in fat and high in protein and carbohydrate. The favorable results in the treatment of cirrhosis reported by Patek[14, 15] cannot be attributed to a single nutrient factor. The diet he recommended was a high protein, high carbohydrate, rich in lipotropic factors, supplemented by vitamin B complex.

VITAMIN DEFICIENCIES

Experimental and postmortem evidence indicates that the liver is a great storage depot for the fat-soluble vitamins A, D, and K. The liver is also known to be instrumental in the formation and storage of the water-soluble vitamins B_1, B_2, and C.[24] Faulty metabolism of the fat- and water-soluble vitamins in the presence of hepatic damage is demonstrable by laboratory tests and clinical signs.

In the treatment of hepatic disease, therefore, the use of vitamin supplements is clearly necessary. From 30 to 50 Gm. of brewers' yeast in tomato juice should be given daily, and enough multiple vitamins in capsules to supply twice the estimated normal adult requirement of vitamins A, C, and D, thiamine, niacin (or the amide), and riboflavin. If there are hemorrhagic symptoms and prolongation of prothrombin time, vitamin K, should be given either orally or parenterally. Bile salts are only necessary when a fat-soluble vitamin K preparation is given orally.

ANEMIA

The anemia that accompanies hepatic disease is due in part to the inability of the damaged liver to store the erythrocyte-maturation factor. In the treatment of this anemia the intramuscular administration of 3 cc. of crude liver extract every other day or twice a week has proved beneficial, as has the daily administration of 1 Gm. of iron gluconate.

SUMMARY

Modern nutritional therapy may arrest, if not reverse, the early pathologic changes accompanying cirrhosis of the liver. In any event, cirrhosis, especially if treated in the early stages, is no longer hopeless.

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* The Council on Pharmacy and Chemistry of the American Medical Association has concluded that, though "no claims for methionine may be recognized at this time . . . careful clinical trial of this agent . . . should be made."

The therapeutic diet in cirrhosis should provide 2500 to 3000 calories a day; 115 to 135 Gm. of protein; 350 to 400 Gm. of carbohydrate; and 100 to 170 Gm. of fat. The diet should be supplemented with brewers' yeast (15 to 25 Gm.) in tomato juice or milk twice daily. This will supply vitamin B complex, and since brewers' yeast is half protein, it is an admirable extra source of that food component. If brewers' yeast is not tolerated a preparation of vitamin B complex should be substituted.

The daily administration of thiamine chloride and crude liver extract (3 cc. intramuscularly) twice or three times weekly has also been recommended.

For patients with ascites, only moderate restriction of fluids but marked restriction of salt is necessary. Mercurial diuretics are good adjuvants to abdominal tappings.

GALLBLADDER DISEASE

In chronic cholecystitis, medical treatment should always be given a trial, except in surgical emergencies. If such treatment fails to relieve the dyspepsia, the persistent local pain, and the general state of illness characteristic of chronic cholecystitis, surgery is indicated. The treatment of cholelithiasis, on the other hand, especially when dyspepsia, flatulence, or frequent pain accompanies the disorder, is almost always surgical.

The medical management of cholecystitis attempts to restore the normal physiology of the gallbladder. In the main, the function of the gallbladder is to store the bile secreted between meals and to equalize the pressure within the biliary passages. The gallbladder and the common bile duct, equipped with smooth muscle and elastic tissue, expand and contract rhythmically. When the gallbladder contracts, the pressure within both it and the common bile duct is raised, and the bile in the gallbladder is discharged through the cystic and the common bile ducts into the duodenum. It is when food from the stomach enters the duodenum that the gallbladder contracts and is evacuated. The contraction is induced by cholecystokinin, a physiologic hormone formed when fats, acid fruits, or gastric juices reach the duodenum. Fats in the form of cream, butter, and egg yolk not only encourage the production of cholecystokinin, but also tend to relax the sphincter of Oddi in the common bile duct and so increase the motor activity of the biliary tract. The filling and emptying of the gallbladder is interfered with when the sphincter of Oddi is in a state of spasm—hypertonic dyssynergia—and resistance is thus offered to contraction of the gallbladder, or when that organ is atonic and suffers from reduced contractibility—hypotonic dyssynergia. In hypertonic dyssynergia the wall of the gallbladder is thickened; in hypotonic dyssynergia it is thin and atropic. In both states, unless proper steps are taken, bile stasis occurs and calculi are likely to form.

Biliary dyssynergia, particularly the hypertonic form, is often difficult to diagnose, since it may simulate cholelithiasis or coexist with it.

In the treatment of noncalculous cholecystitis three goals are to be achieved: (1) the elimination of foci of infection; (2) the prevention of stasis and the promotion of the free flow of bile; and (3) the relief of dyspepsia and spasm. Control of the patient's diet is of great importance. As Rehfuss puts it: "By means of the diet, we can either splint the gallbladder and set it more or less at rest, or we can stimulate the organ to increased function."

Hypertonic Dyssynergia (Biliary Dyskinesia)

Hypertonic dyssynergia with spasm of the sphincter calls for a bland diet containing a minimum amount of fat. Severe restriction of the dietary fat, however, is to be avoided, since such restriction often invites stagnation of the bile in the gallbladder. Patients vary as to the amount of fat they can tolerate without distress. A minimum amount of dietary fat, then, means less fat than the patient can comfortably tolerate.

The low-fat diet should be supplemented with the fat-soluble vitamins A, D, and K. Alcohol, highly seasoned foods, spices, pickles, and condiments; greasy and fried foods; fatty meats like pork and sausage; fatty fish like herring, mackerel, salmon, and sardines; fatty cheeses; rich dressings; cream soups and nuts should be avoided. The value of small meals and a bland, nonirritating, low-residue diet was stressed by Twiss and Green.[22] Dietary treatment supplemented with antispasmodics (belladonna, syntropan, and novatropine) will be found useful in the treatment of noncalculous cholecystitis. Small doses of phenobarbital may prove helpful, too, since emotional disorders often underlie spasm of the sphincter of Oddi. Certainly sufficient sleep, exercise, play, and fresh air are to be prescribed, and an attempt should be made to free the patient's mind from worry.

Hypotonic Dyssynergia

Hypotonic dyssynergia, or chronic noncalculous gallbladder disease with a poorly functioning hypotonic organ without acute symptoms, calls for a stimulating diet. Fats and oils best encourage the emptying of the biliary tract. It is often effective in treating patients with hypotonic dyssynergia, to prescribe olive oil to be taken between meals or upon waking. Since a high-fat diet often proves upsetting, however, the patient's fat tolerance should be determined before it is prescribed for him.

The high-fat diet includes milk, cream, butter, and eggs; these make it palatable and supply vitamins A and D. The protein in the diet for patients suffering from hypotonic dyssynergia should amount to about 80 Gm. per day, for protein is needed in the formation of bile salts. Such patients may therefore be permitted moderate quantities of lean beef, mutton, chicken, and white fish.

They should be encouraged to eat small meals, not to skip meals, to avoid foods that disagree with them, and to imbibe large quantities of liquids—on getting up, between meals, and on going to bed.

Cholesterol in the Diet

Although most gallstones contain cholesterin, there is no evidence of correlation between the dietary cholesterol and the cholesterin in the bile. Even though the diet contains no cholesterol, endogenous cholesterol-metabolism proceeds. A high cholesterol concentration appears in the blood and bile of pregnant women. Whether this explains the frequent association of gallbladder disease and gallstones with pregnancy cannot, however, be stated with certainty. In the presence of hypercholesteremia it would seem wise to prescribe a diet poor in cholesterol, and this whether the diet is a low-fat or a high-fat one. Foods rich in cholesterol are egg yolk, liver, sweetbreads, oysters, fish roe, and lard.

Obesity

Since patients with gallbladder disease are often overweight, they should be given a reducing diet, which alone may improve their condition.

Stimulation of the Flow of Bile

Foods rich in fat, especially butter, cream, and olive oil, promote the flow of bile. Where this is desirable, some clinicians advocate the use of bile salts (sodium glycocholate, sodium taurocholate, or the salts found in fel bovis) in addition to a high-fat diet. Ivy,[9] however, has shown that bile salts have no effect on the emptying of the gallbladder. Nevertheless, the administration of sodium dehydrocholate brings about the flow of thin liver bile. Ivy and his associates[9] have shown that cholic and desoxycholic acids increase the production of natural bile acid and the secretion of cholesterol and pigment. Bile salts, then, it is safe to conclude, are particularly useful, in combination with a high-fat diet and an antispasmodic, in relieving bile stasis. Dilute hydrochloric acid is helpful in cholecystic disease, particularly "lazy gallbladder," in which there is little or no gastric acidity. In hyperacidity, alkali powders (calcium carbonate with calcined magnesia or bismuth subcarbonate) will be found useful.

ELIMINATION

Since saline cathartics (sodium phosphate and magnesium sulphate) tend to relax the sphincter of Oddi and permit the flow of bile, they are especially effective in chronic biliary conditions involving mild spasm of the sphincter. Every spa therapy owes much of its reputation to the saline catharsis of the mineral salts of the spa waters.

BIBLIOGRAPHY

1. ALMY, T. P. The use of protein hydrolysates. *Am. J. Med.* 3:483, 1947.
2. BOCKUS, H. L. Gastro-Enterology. Philadelphia, Saunders, 1946, Vol. 1, p. 437.
3. BRUCH, H. Psychiatric aspects of obesity in children. *Am. J. Psychiat.* 99:752, 1943.
4. ELMAN, R., and HEIFETZ, C. J. Experimental hypoalbuminemia. *J. Exper. Med.* 73:417, 1941.
5. GETZ, H. R., and KOERNER, T. A. Vitamin nutrition in tuberculosis. *Am. Rev. Tuberc.* 47:274, 1943.
6. GETZ, H. R. Nutrition and tuberculosis. *Nutrition Rev.* 5:47, 1947.
7. GRAY, S. J. Management of patients with massive hemorrhage from peptic ulcer. *M. Clin. North America* 31:470, 1947.
8. HOAGLAND, C. L. Therapy of liver diseases. *Bull. New York Acad. Med.* 21:537, 1945.
9. IVY, A. C. The effect of therapeutic agents on the volume and the constituents of bile. *Am. J. Digest Dis.* 5:613, 1938.
10. LABBY, D. H., SHANK, R. E., KUNKEL, H. G., and HOAGLAND, C. L. Cirrhosis of the liver. *J.A.M.A.* 133:1181, 1947.
11. LONG, E. R., quoted by CANNON, P. A. Advances in Protein Chemistry. New York, Academic Press, Vol. II, 1945.

11a. MACHELLA, T. E. *Am. J. Med.* (in press).

12. MEULENGRACHT, E. Medical treatment of peptic ulcer and its complications. *Brit. M. J.* 2:321, 1939.
13. MILLER, L. L., ROSS, J. F., and WHIPPLE, G. H. Methionine and cystine specific protein factors preventing chloroform liver injury in protein-depleted dogs. *Am. J. M. Sc.* 200:739, 1940.

14. Patek, A. J. Jr. Treatment of alcoholic cirrhosis of the liver with high vitamin therapy. *Proc. Exper. Biol. & Med.* 37:329, 1937.
15. Patek, A. J., Jr., and Post, J. Treatment of cirrhosis of the liver by a nutritious diet and supplements rich in vitamin B complex. *J. Clin. Investigation* 20:481, 1941.
16. Ravdin, I. S. The protection of the liver from injury. *Surgery* 8:204, 1940.
17. Ravdin, I. S., *et al.* The prevention of liver damage. *J.A.M.A.* 121:322, 1943.
18. Ruggiero, W. F., Co Tui, F., and Bianco, A. A. Management of ambulatory peptic ulcer patients with protein hydrolysate. *New York State J. Med.* 46:2395, 1946.
19. Selling, L. S., and Ferraro, Mary, A. The Psychology of Diet and Nutrition. New York, Norton, 1945.
20. Shaffer, P., and Coleman, W. Protein metabolism in typhoid fever. *Arch. Int. Med.* 4:538, 1909.
21. Thorn, G. W., *et al.* Chemical and immunological studies on products of human plasma fractionation: Use of salt-poor concentrated human serum albumin solution in treatment of hepatic cirrhosis. *J. Clin. Investigation* 25:304, 1946.
22. Twiss, John R., and Green, C. H. Dietary and medical management of diseases of the gall bladder. *J.A.M.A.* 101:1841, 1933.
23. Wohl, M. G. Nutrition, disease and psychology. *Pennsylvania Med. J.* 51:654, 1948.
24. Wohl, M. G., and Feldman, J. B. Vitamin A deficiency in diseases of the liver: its detection by dark adaptation method. *J. Lab. & Clin. Med.* 25:485, 1940; The occurrence of avitaminosis A in diseases of the liver. *Am. J. Digest. Dis.* 8:464-469, 1941.

Chapter 27

DIETOTHERAPY (Continued)

Michael G. Wohl and Norman G. Schneeberg

CARDIOVASCULAR DISEASE

Although the prime object of diet therapy in heart disease is normal nutrition, two additional objectives must be considered in choosing the diet for the patient suffering from cardiac failure: reducing the heart's work and preventing or eliminating edema.

Reducing the Work of the Heart; the Semistarvation Diet

If the work of the heart is to be reduced, the elevated basal metabolic rate associated with cardiac failure must be lowered; and if the patient is overweight, his weight must be brought down to normal or slightly below normal. In heart failure the rise in the basal metabolic rate is probably due to the rise in muscular work caused by cough or dyspnea. Although bed rest and the use of digitalis and diuretics may reduce the metabolic rate, caloric restriction is usually necessary, too, to achieve that end. In certain studies of the effects of dietary restriction it was found that, as a result of such restriction, patients of normal weight showed a drop in oxygen consumption, basal metabolism, pulse rate, and blood pressure, and obese patients a reduction of 16 per cent in oxygen consumption, 30 per cent in cardiac output, and 35 per cent in cardiac work. It seems, therefore, that for a patient with moderate or severe congestive heart failure the initial stages of therapy require a low-calorie diet.

The popularity of the Karell diet in the treatment of cardiac failure is based on the fact that it is low in calories, poor in salt, and low in protein. It consists of 200 cc. of skim milk administered four times a day—at 8 A.M., noon, 4 P.M., and 8 P.M. It supplies 28 Gm. of protein and only 287 calories. The patient tolerates this semistarvation diet well for forty-eight hours or more. During the first twenty-four or forty-eight hours the diet may bring about beneficial diuresis and relief of symptoms.

When the patient improves and desires substantial food, he is given cereals, whole milk and cream, fruit juices (in limited quantity), soft-boiled eggs, toasted white bread, puréed vegetables, jello, junket, custard, and baked apple (Appendix Table D). All coarse and irritating foods, all gas-producing foods (such as cabbage, cauliflower, radishes, potatoes, and carbonated beverages), all condiments, all salty and pickled foods, and all fried and greasy foods are eliminated.

Proger and Magendantz[13] have employed the Karell diet in the initial treatment of severe congestive failure. They have followed it with a 356-calory diet for a week. Then, until a 10 per cent loss of weight (exclusive of edema fluid) was effected in the patient, they have prescribed a 600-calorie diet. They have then maintained the patient's modified weight with 1100- and 1200-calorie diets. The caloric intake requires adjustment, of course, in cases of obesity or extreme leanness.

PREVENTING OR ELIMINATING EDEMA; THE LOW-SALT, ACID-ASH DIET

For the prevention or elimination of edema in cardiac failure, a low-salt, acid-ash diet is required. This diet is outlined on page 659. In the past, fluids were limited in heart failure to 1000 or 1500 cc. a day while the use of salt was only casually restricted. It is known now that a low-sodium diet in which the fluid intake is not limited at all will prevent edema or, if edema already exists, help eliminate it, whereas increasing the salt intake of patients recovering from heart failure will produce a clinical condition indistinguishable from congestive heart failure.

The fundamental mechanism involved is probably related to a retention of sodium that results in the accumulation of extracellular fluid.

LOW-SODIUM, ACID-ASH DIET, CALORIES UNRESTRICTED*

Foods unrestricted as to amount, at least two or three servings must be taken daily:

Eggs: Two equal one serving (may be substituted for a meat serving).
Meats: Meat, fish, or chicken; one serving of about 120 Gm. a day.
Bread: Plain breads without nuts or raisins; whole wheat bread preferable (5 slices, or comparable amount of cereal foods as substitutes, each day).
Cereal: These only (one serving a day at least): Oatmeal, farina, quick-cooking cream of wheat, cracked or ground whole wheat, cornmeal mush, hominy, puffed rice or puffed wheat, "Muffets."
Cereal Foods: Macaroni, spaghetti, rice, home-made noodles, corn may be served at any meal; imperative if meat or eggs is not eaten.
Fruit: Prunes, plums, and cranberries.

Foods restricted as to amount (no more than two servings should be taken):

Vegetables: Two servings a day or ½ cup each of any vegetables (except parsnips, lima beans, rhubarb, chard, and spinach, which are forbidden). One small potato equals a serving. Use fresh or frozen vegetables or those canned without salt.
Fruit: One serving of ½ cup of fruit or fruit juice daily; no raisins or dates.
Milk and Milk Products: Two cups of milk daily, including that used in preparing food. Cream: 2 tablespoons in coffee or tea, ¼ cup for breakfast cereal. Ice cream: without fruit or nuts, one small scoop a day. Cheese: only unsalted cottage cheese (which may be substituted for a meat or egg serving).

Other foods and food combinations:

Soups: Vegetables as allowed above may be combined with milk allowance or with salt-free broth to make soups. Salt-free clear beef or chicken broth may be taken as desired, both with and between meals.
Desserts: No limit as to amount: plain jello, wine jelly, plain tapioca, angel food or sunshine cake (no cake or cookies made with salt, soda or baking powder). *Limited* by milk allowance above: custard, junket, cornstarch pudding, egg-nog, ice cream. Fruit as indicated above.
Beverages: One cup of tea or coffee at each meal; chocolate made with milk allowance.
Neutral foods: To be taken in any quantity desired: sugar, butter, oil, gelatin, salt-free salad dressing, plain tapioca and plain cornstarch, clear sugar candies.

* After Schemm; *Ann. Int. Med.* 17:962, 1942.

HIGH-PROTEIN, LOW-SODIUM, HIGH-POTASSIUM, ACID-ASH DIET FOR USE IN EDEMA*

Fruit: Three servings daily, fresh or stewed, but should include either prunes, plums, cranberries or currants once daily.

Vegetables: Two large servings daily, especially beets, carrots, Brussels sprouts, yellow corn, kohlrabi, lettuce, mushrooms, peas, spinach, kidney beans, parsnips.

Meat: Two servings daily.

Eggs: Two.

Milk: One glass.

Cream: One glass.

Butter: Salt-free, 6 squares.

Cereal: Oatmeal or wheatena; farina, puffed wheat or rice occasionally.

Bread: Graham bread, 3 large slices or 6 small slices daily.

Rice, macaroni or spaghetti: One serving daily.

Potato: One serving.

Jelly, preserves or honey: Two level tablespoons.

Sugar: *Ad libitum*—at least 1 tablespoon.

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* After Barker (from Wohl).

SOURCES OF SODIUM TO BE AVOIDED

I. Salt, both in food preparation and cooking and at the table.

II. Commercially processed foods to which salt has been added. These include:

   1. Smoked, salt-cured, and other processed meats, such as ham, bacon, salt pork, sausages, corned beef, salt fish, canned meats and fish, bouillon cubes and meat extracts.
   2. Cheese.
   3. Pickled and spiced products, such as olives, pickles, catchup, sauces, salad dressings, and prepared mustard.
   4. Canned vegetables, soups, meats, and fish, unless salt free.
   5. Salted butter and margarine.
   6. Ordinary bakery goods and crackers *except* low-sodium bread, low-sodium caraway seed bread, low-sodium cinnamon roll, Passover bread (matzoth).
   7. Many prepared cereals except pearled barley, corn meal, cracked wheat, plain farina, Instant Ralston, Oatmeal (rolled oats), puffed rice, puffed wheat, shredded wheat, wheat germ, wheatena.
   8. All other salted foods, such as pretzels, potato chips, popcorn, salted nuts, and many candies and candy bars.

III. "Soda" products, such as baking soda (sodium bicarbonate), baking powder, and self-rising flours, including pancake, biscuit, muffin and cake mixes; also various laxatives and other remedies containing "salts."

Where loss of edema does not follow a restricted intake of sodium, the use of a neutral or acid-ash diet will prevent neutralization of metabolic acids and mobilize the fixed base (sodium) of the body.

Increasing the water intake of patients with cardiac failure is a rational means of combating the dehydration that so often accompanies that disorder and of insuring adequate urine formation and the excretion of sodium and water.

The acid-ash, salt-poor diet consists mainly of meat, chicken, fish, eggs, wheat products, and bread. Foods that yield an alkaline ash, such as milk, vegetables and fruits (except cranberries, plums, and prunes), are restricted. The amount of sodium as sodium chloride is limited to from 1 to 1.5 Gm. a day. Such a diet is planned as follows: (1) Foods of low salt content are chosen. Salt-poor bread, sweet butter, salt-free salad dressings and canned goods are used. Vegetables are boiled twice and the first water discarded. (2) No salt is used as seasoning. A salt substitute must serve. (3) The extra fruit so often supplied the patient by well-meaning visitors is forbidden. (4) All salty appetizers, salty biscuits, potato chips, etc., are eliminated. (5) Soda, baking powder, and all sodium-containing medicines are forbidden. Fluids may be permitted *ad lib.*[*]

The low-sodium, acid-ash diet aids in the control of edema that has resisted the effects of digitalis, diuretics, and moderate restriction of salt and fluid. It eliminates the need for fluid restriction and the frequent use of mercurial diuretics. Owing to its unpalatability, however, and the need for extreme care in its preparation and rigid supervision of its employment, the applicability of this regimen is limited to selected cases; but where it can be used without great difficulty and the patient tolerates it well, the low-salt, acid-ash, and fluid *ad lib.* treatment of congestive heart failure proves most effective.

HEART DISEASE WITHOUT FAILURE

The selection of a good diet for the patient with compensated heart disease may be necessary for his comfort and freedom from symptoms. In general, the diet is liberal and includes all foods that any other well-balanced diet contains. The caloric intake should be calculated to maintain a weight just below normal. Reducing the obese cardiac patient to normal weight is the most important part of the therapy. Feedings may have to be smaller than for a person in health; and, in order to insure an adequate caloric intake, four or five small meals a day may be necessary, although most cardiac patients do well on the ordinary three-meal schedule. Gas-forming foods, highly spiced and pickled foods, and fried and greasy foods usually must be eliminated. The cardiac patient learns to choose foods that he can tolerate, but he requires dietary guidance for good nutrition.

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[*] The average cardiac patient permitted fluids *ad lib.* consumes approximately 1700 cc. daily during the summer, 1300 cc. in winter, and 2200 cc. when febrile.

The patient with coronary artery disease (angina pectoris, coronary insufficiency, previous myocardial infarction) represents a special problem in diet therapy. Distension of the stomach, it has been shown, reduces the coronary blood flow; and after a heavy meal, an increase in cardiac output occurs. Hence, moderation in eating may be necessary to prevent attacks of anginal pain.

Hypercholesteremia

The pathogenesis of arteriosclerosis is still unknown, but several investigators have emphasized the role that hypercholesteremia may play in its etiology. Leary,[8] for example, succeeded in producing arteriosclerosis in rabbits by feeding them diets high in cholesterol; arteriosclerosis could be produced in carnivorous animals by means of a high-cholesterol diet with thyroid depression. Striking are clinical histories that reveal diets excessively rich in eggs, sour cream, butter, and ice cream, or in milk (up to 1500 cc. daily), in patients with myocardial infarction before the age of 50 who are neither diabetic nor hypertensive.

The following items are omitted from a low-cholesterol diet (Appendix Table D): butter, lard, suet, egg yolk, fatty fish, fish roe, oysters, liver, kidneys, brain, sweetbreads, goose, duck, sausage, pork, bacon, and all fats. There is as yet no clear evidence to show that low-fat diets will prevent arteriosclerosis or its complications in man.

Acute Coronary Thrombosis

After an acute myocardial infarction, the patient's diet is limited to water, clear soups, fruit juices, and milk for the first two or three days after the episode. As the patient recovers, his diet is gradually liberalized in a manner similar to the diet of patients with acute congestive failure.

ESSENTIAL HYPERTENSION

Until recently the effective use of diet therapy in essential hypertension has been confined to the reduction of excess weight. A significant weight reduction may be accompanied in some patients by a lowered blood pressure. Occasionally there is a striking return to normal from mild hypertensive levels.

Certain experimental and clinical observations have revived interest in

Allen's early suggestion[1] for combating essential hypertension with a low-salt diet, an approach that for more than twenty years attracted little clinical enthusiasm. Today there is some suggestive evidence that the limitation of sodium chloride intake to less than 1.2 Gm. a day will reduce the blood pressure in an appreciable proportion of patients and relieve some symptoms of hypertension, such as headache.

Kempner[7] recommends treating the hypertensive patient with a rice, sugar, fruit, and fruit-juice diet, supplemented by vitamins and iron.

KEMPNER RICE-AND-FRUIT DIET FOR HYPERTENSIVE PATIENTS

(Protein, 20 Gm.; Carbohydrate, 460 Gm.; Fat,
5 Gm.; Sodium, 0.2 Gm.; Chloride, 0.15 Gm.)

The diet consists of rice, white or brown, boiled carefully for twenty minutes, served hot and relatively dry; approximately 230 Gm. a day in three courses with fresh or frozen fruits of nearly all kinds, and sugar more or less *ad lib.* to bring the total calories to 2000 or somewhat more. Between meals, munching on rice-brittle candy is permitted. No meat, vegetables, milk, or salt is allowed for the first six weeks or so, and then the diet may be gradually liberalized with 2 potatoes and a few ounces of meat weekly. Later, if the blood pressure stays down, one-third of the fruit is replaced by vegetables and more meat is given.

The patient should receive daily, as minimal doses: vitamin A, 5000 units; vitamin D, 1000 units; thiamine chloride, 5 mg.; riboflavin, 5 mg.; niacinamide, 25 mg.; calcium pantothenate, 2 mg.; and ferrous sulfate, 0.6 Gm.

This is essentially a low-sodium, low-protein diet. The favorable results he has achieved with this diet have been confirmed to some extent in experiments with dogs. It is claimed that despite the low protein intake, the protein equilibrium of the patients on the rice diet is maintained.

The low protein content of the diet (20 Gm. a day) probably contributes to the reduction of the blood pressure. The Kempner rice-and-fruit diet therefore seems at least worthy of serious investigation in the therapy of hypertension. An important point that has been recently stressed, however, is the possibility of the development of azotemia due to hypochloremia and the danger of liver damage incident to the low protein content of the diet. It is our opinion that we should withhold the introduction of this regimen into general practice until its value has been firmly established by investigations now under way in various institutions.

NEPHRITIS

The effect of diet on the course of nephritis has been the subject of much conflicting experimental and clinical work. Although it seems unlikely that the essential progress of nephritis can be arrested by dietary means, the various secondary manifestations of the disorder may be partly or even wholly controlled through a rational diet aimed at the metabolic disturbances that cause them.

Dietary adjustments during the course of the disease depend on whether edema, hypoalbuminemia, hypertension, cardiac failure, acidosis, or azotemia exist either singly or in various combinations.

When edema complicates nephritis, the cause may be either retention of sodium and water, owing to the inability of the damaged kidney to excrete enough sodium; or hypoalbuminemia; or cardiac failure; or all three.

Since the damaged kidney may be unable to maintain sodium balance on a salt intake even so low as 2 to 5 Gm. a day, drastic reduction of the salt intake may be necessary. To promote reduction of the edema by helping the kidney to eliminate sodium, it is advisable to prescribe an acid-ash diet.

Hypoalbuminemia, a frequent finding in the nephrotic stage of nephritis and not uncommon—though less severe—in the acute stage, requires an attempt to build up the depleted serum and tissue protein by increasing the daily protein intake to 2 or 3 Gm. per Kg. of body weight. This may be done through a high-protein diet, protein hydrolysates, blood plasma, and, if available, salt-poor human serum albumin.* Although the serum albumin levels are rarely restored to normal, the stores of tissue protein usually are, and the patient's sense of well-being is increased.

How much protein should be included in the diet of nephritic patients remains in dispute. Most studies indicate that a good deal of it, far from being harmful, may improve the patient's clinical status, but some evidence has been adduced that protein is harmful in nephritis. It is generally recognized, however, that the protein intake must be increased when hypoalbuminemia complicates the disorder.

In nephritis complicated by edema, therefore, an acid-ash diet low in sodium and high in protein should be prescribed. When acidosis is the complicating factor, however, an acid-ash diet cannot be used, and base must be supplied by an alkaline-ash diet supplemented as necessary by cautious intravenous administration of sodium bicarbonate or sixth-molar sodium lactate. If both edema and acidosis occur, excess base must still be supplied. An alkaline-ash diet relatively high in protein is advocated.

When azotemia is the complicating factor, however, the daily protein intake should not exceed 0.75 or 1 Gm. per Kg. of body weight.

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* Current reports indicate that human serum albumin may be used with striking and encouraging effect in cases of hypoalbuminemia; but the cost of the preparation is almost prohibitively high.

LOW PROTEIN DIET*

The following is an outline of a low-protein diet for the average patient in bed. It provides approximately 40 Gm. of protein, 1500 calories, 1200 to 1400 cc. of water (in the food), and 7 to 8 Gm. of salt (2 or 3 Gm. naturally present in the food, 5 Gm. added during preparation). Up to 1200 cc. of additional fluid is allowed.

If salt restriction is in effect, use sweet butter. To increase the protein value to 60 Gm., add 85 Gm. of meat, any kind except salt meats or fish.

Breakfast

1 serving of fruit
1 serving of cereal
1 egg
1 cup of 20% cream
1 teaspoon of butter
1 slice of bread

Dinner

1 cup of cream soup
1 serving of potato
2 servings of vegetable
1 salad
1 serving of fruit
4 teaspoons of cream
1 slice of bread
2 teaspoons of butter

Supper

2 servings of vegetable
1 serving of salad
1 serving of fruit
4 teaspoons of cream
1 slice of bread
2 teaspoons of butter

* After Bortz (from Wohl).

This will meet the patient's nutritional needs without putting an additional burden on his kidneys. If the patient with chronic nephritis is obese, his weight should be reduced to normal.

Alcoholic beverages should be forbidden to patients with nephritis, although there is no evidence to show that a little at infrequent intervals will do them harm.

Anorexia, nausea, and vomiting often interfere with nutrition in the acute stage of glomerulonephritis. If the patient can take fluids by mouth, however, he may be maintained for several days with water, milk, fruit juice, and lactose.

METABOLIC DISEASES

The close functional relationship between nutrition and metabolic disorders has been demonstrated by both experimental and clinical work. The analogous physiologic effect of vitamin D and the parathyroid hormone on the skeletal system, for example, illustrates that relationship admirably, as does the fact that the capacity of the liver to inactivate estrogens is inhibited by a diet deficient in the vitamin B complex. The clinical signs of excess estrogen observed at times in cirrhosis of the liver—menorrhagia in women and gynecomastia in men—may be a direct consequence of vitamin B deficiency.*

Another example of the connection between nutrition and metabolism is the interrelationship of certain nutrient factors and the thyroid hormone—both of significance in energy metabolism. There is experimental evidence of an antagonistic action between certain vitamins (A, B, and C) and the thyroid hormone. In hyperthyroidism, therefore, unless the intake of accessory food factors is large, conditioned vitamin deficiency may complicate the picture.

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* The adrenal gland, through its cortical hormones, has been found to be involved in both riboflavin and pantothenic acid deficiencies. (Agnes Fay Morgan, Abstracts of Papers, American Chemical Society. Atlantic City, September 18-23, 1949.)

HYPERTHYROIDISM

In the treatment of hyperthyroidism it is therefore important to plan the patient's diet so as to prevent or correct vitamin and other nutrient deficiencies.

CALORIC INTAKE

The thyrotoxic patient uses up much more than the normal amount of energy and does all his muscular work inefficiently. Weakness and extreme loss of weight are common effects. The daily energy intake of the thyrotoxic patient, therefore, should be high—often in the neighborhood of 4000 to 4500 calories. Gain of weight shows that the patient is getting calories enough to meet his increased energy requirement.

PROTEIN

There is evidence that a high level of nitrogen excretion accompanies hyperthyroidism; and as a result of the disorder, too, the liver and muscle protein may be greatly reduced. The daily diet of the hyperthyroid patient should therefore include not less than 1.5 Gm. of protein per Kg. of body weight. Much more protein is permissible; but if the caloric intake is high, 1 Gm. of protein daily per Kg. of body weight will prevent protein depletion and suffice to maintain nitrogen balance.

CARBOHYDRATE

When metabolism is accelerated, the glycogen in the liver and in other body depots tends to become depleted; and, concomitantly, the liver becomes increasingly vulnerable to hepatotoxic agents. A liberal supply of carbohydrate (400 to 500 Gm. daily) is therefore indicated.

FAT

To meet the rest of his caloric requirement, the thyrotoxic patient should be given fat; for, if he gets enough carbohydrate, his fat oxidation is normal. Milk, cream, butter, and eggs are good sources of the needed fat. He should not be given too much fat, however, since in excess it is likely to cause diarrhea.

WATER

DuBois and Soderstrom[5] found that patients with severe or moderately severe hyperthyroidism lost about 40 Gm. of water an hour through the skin and the lungs, compared to a loss of 25 to 30 Gm. by normal subjects. It is evident that the thyroid patient requires an abundant supply of water.

VITAMINS

It has been observed that hyperthyroid patients given thiamine chloride preoperatively show a more rapid decline in pulse rate than do patients not so treated.

Lack of thiamine, furthermore, leads to loss of both appetite and weight. On the other hand, the administration of sufficient amounts of the B complex, according to experiments with hyperthyroid animals, prevents loss of weight even in the presence of hypermetabolism. The application of the experimental observations here has shown that hyperthyroid patients given thiamine gain weight more rapidly than do patients not given thiamine preoperatively.

The increased thiamine chloride requirement is proportional to the increase in the basal metabolic rate and the sum of the caloric intake. In hyperthyroidism, the utilization of sugar and starch is accelerated, and the oxidation of glucose in the tissues is stepped up. And since thiamine, riboflavin, and nicotinic acid are concerned with that oxidation, there is an additional reason for prescribing an increased supply of these vitamins for hyperthyroid patients. It has also been shown that muscular weakness in hyperthyroidism may be improved to a significant degree by the administration of vitamin B_6 (pyridoxine) (see Chapter 24).

The hyperthyroid patient, whether he is under medical treatment with propylthiouracil or iodine, or is being prepared for surgery, should consume great quantities of milk, not only for the fat it contains but also for the calcium. He should eat eggs and dairy products; meat, fish, and fowl; all vegetables, including potatoes; cereals and bread; fresh fruits and fruit juices; jellies and marmalades; ice cream, custard, junket, and rice pudding. Double portions of these foods may be allowed him at the three regular meals of the day, and his diet may be supplemented morning, noon, and night with a sandwich and a dessert. In between the interval feedings, he may be permitted to drink milk or a fruit juice. It is of the utmost importance that he have more than enough food every day to satisfy his increased caloric requirement. The diet should be supplemented with 10 to 20 mg. daily of thiamine chloride and brewers' yeast. Such a nutritional program is maintained until the thyrotoxic state is adequately controlled. The hyperthyriod patient should not drink coffee, tea, or alcoholic beverages. And he should either not smoke or be limited to a single cigarette after each of the day's three main meals.

ADDISON'S DISEASE

Addison's disease is caused by loss of functioning adrenocortical tissue as a result of tuberculosis, atrophy, tumor, or hypopituitarism. The manifestations arise from lack of one or more of three known groups of essential steroid hormones or possibly from lack of as yet unidentified adrenocortical factors.

Underproduction of desoxycorticosterone-like hormones is followed by renal inability to retain sodium; and this results in a negative sodium and water balance. Deficiency in a second group of steroid hormones—the 11 oxy-steroids, corticoids (Selye), or the sugar hormones (Albright)—prevents the manufacture of glucose in the body from stores of protein and perhaps from fat as well. Hence, if readily available carbohydrate is not supplied, hypoglycemia may result. And deficiency in the adrenal androgens, or N hormones (Albright), may be responsible for excessive protein catabolism or antianabolism, with attendant loss of protein-tissue stores.

The dietary treatment of Addison's disease must be directed toward the amelioration of these metabolic disturbances. In some patients, merely increasing the salt intake may be enough to correct the electrolyte metabolism. From 10 to 15 Gm. of sodium chloride may be administered to such patients in enteric-coated tablets at meal times. For the patient who has difficulty in swallowing pills, the salt may be measured into a shaker in the morning and used on food throughout the day; or it may be taken in a solution such as the following one outlined by Lukens:[9]

Sodium chloride	10 Gm.
Sodium citrate	5 Gm.
Lemon juice	80 cc.
Sugar	160 Gm.
Cold water, to make	1000 cc.

If a diet low in potassium is prescribed, this salt ration may be reduced.

Most patients require desoxycorticosterone in addition to salt to maintain normal electrolyte stores. The dose must be carefully regulated, for overdosage may produce edema, hypertension, cardiac failure, and neuromuscular signs of hypopotassemia. If the dosage of desoxycorticosterone acetate is kept at a minimum, maintenance can often be accomplished by varying the intake of sodium chloride. McGavack and Babcock have advocated the use of diets with a sodium content so accurately ascertained that desoxycorticosterone acetate can be given in maximum therapeutic doses without risk of complications. This is feasible with an intelligent and cooperative patient, especially if he takes all his meals at home. When desoxycorticosterone acetate is being administered, a diet low in potassium is contraindicated because of the likelihood of hypopotassemia and the resulting disturbances in sodium-potassium ratio.

The patient with Addison's disease often finds it hard to fast. Thorn reported that 26 of 52 patients experienced episodes of spontaneous hypoglycemia. Such patients require frequent high-protein feedings. The absorbed amino acids can be utilized by the patient even though he is unable to mobilize his own protein stores for gluconeogenesis. If frequent high-protein feedings fail to eliminate hypoglycemic episodes, a potent adrenal cortical extract must be administered.

The protein anabolic effects of testosterone have been utilized in the treatment of Addison's disease to accelerate weight gain and recovery of strength. Testosterone, however, cannot replace whole adrenal extract where hypoglycemia, low stress resistance, and lack of endurance obtain.

The patient with adrenocortical failure is in a poor nutritional state and requires a diet rich in calories, protein, and vitamins. But because distressing anorexia, nausea, and vomiting, often provoked by the mere sight or smell of food, plague him, insuring an adequate food intake poses a therapeutic problem. It can be solved only when the metabolic disturbances of the disease have been improved by treatment with potent steroid hormones and parenteral saline and glucose. Even so, the patient's appetite is inconstant and his diet must cater to his whims. Liquid and light feedings must be served him until he can tolerate a full, solid diet. Even when hypoglycemia does not complicate the picture, most patients with Addison's disease require smaller and more frequent feedings than healthy persons. Three small meals a day with interval and bedtime feedings should be effective. Protein concentrates have proved useful when a good protein intake could not otherwise be managed. Their unpalatability can be masked by mixing the powder with milk, fruit juice, tomato juice, or vegetable juices.

GOUT

While the fundamental cause of gout remains obscure, it is known to proceed from a disturbance in the purine metabolism, reflected in the high uric acid content of the blood during the paroxysms. Gout is precipitated by general overeating, overindulgence in foods rich in nucleoproteins and fats, overindulgence in alcoholic drinks (especially malt liquors and wines), and overexercise. Overexercise often precipitates an attack of gout through the increase in endogenous uric acid that accompanies such activity.

The treatment of gout includes limitation of exercise; dietary measures to reduce high uric acid content of the blood; and medicinal agents to evoke rapid elimination of uric acid.

DIETARY MEASURES

The diet in gout must be individualized. If the patient is fat, the caloric intake should be reduced; if he is old and weak, particular attention should be given to the maintenance level. In general, the diet should be normal in protein, rich in carbohydrate, poor in fat, and as free as possible from foods rich in purine bodies, although patients will find it difficult to abide by a purine-free diet for long. The normal diet contains 600 to 1000 mg. of purine daily; a low-purine diet contains only 100 or 150 mg. daily.

The gouty patient should drink large quantities of liquid between meals. Alcoholic drinks, however must be strictly forbidden; and tea, coffee, and cocoa, since they contain methylated purines—thought by some to increase the uric acid in the body—are to be taken only in moderation.

In supplementing the diet with vitamin B complex, it should be borne in mind that the purine content of that complex depends on its source and the degree of its refinement. Since beef liver, for example, contains 233 mg. of purine per 100 Gm., it is not a good source of vitamin B for the gouty patient. Yeast, on the other hand, contains so little purine that it is an excellent source of that vitamin for him.

FOODS FORBIDDEN

The following are contraindicated: kidney, liver, sweetbreads, sardines, anchovies, brains; alcoholic beverages, whole grain products, such as whole wheat bread, shredded wheat, oatmeal; asparagus, beans, cauliflower, peas, soups, meat extracts; butter, cream, mayonnaise, and fat-containing foods.

FOODS PERMITTED

Milk (skimmed), eggs, fruits, vegetables except as listed above; cereals, except whole grain; cottage cheese; breads, except whole wheat; jelly, gelatin; potatoes, rice, macaroni, spaghetti, noodles; cocoa, coffee, Postum, or tea (one cup a day); meat, fish and fowl (amount permitted depending on severity and progress of condition): lean beef, veal, chicken; herring, oysters, crab, cod, whitefish, bluefish, finnan haddie, tuna.

ACUTE ATTACK OF GOUT

During an acute attack of gout,* the diet should be low in calories, low in fat, high in carbohydrate, and as free as possible from purine. Meat and fish should be forbidden, but milk, cheese, and eggs may be permitted. Other permissible foods are fortified margarine, nuts, gelatin, sugar, white bread, cereals, fruits (but not strawberries), and potatoes and other root vegetables. Asparagus and spinach are to be avoided. Fluids should be taken freely.

ALLERGIC DISEASES

In the course of severe allergic diseases, malnutrition may develop as a result of interference with appetite, digestion, or the absorption of nutrients. Bronchial asthma in the young, for example, may result in retardation of growth; nasal allergy may interfere with nutrition through the associated deformation of the dental arch and irregularities of the teeth, jaws, and palate; and gastrointestinal allergy may force the patient to eliminate essential nutrients from the diet.

Where malnutrition is indirectly caused by infirmity attendant upon an allergy, the cure or alleviation of the allergy is the primary objective. Proper attention to nutrition, however, is as important in the treatment of allergic conditions as it is in any other disease process. Although when a patient is in the throes of an acute asthmatic attack his nutritional needs may be safely disregarded for the moment, where protracted asthma obtains, nutritional balance is as important as it is difficult to achieve. The selection of a well-balanced and attractive diet, supplemented as necessary with liquid nutrients, is essential.

Food allergy represents a special problem in nutrition. Diagnosis must be established by eliminating the offending food, and, if that food is an essential dietary constituent, some substitute for it or a means of altering

* Certain drugs have been found useful in promoting the excretion of uric acid in gout. Colchicine, for example, in doses of 0.5 to 1 mg. every hour for four to eight hours, will bring about rapid and often dramatic relief from an acute attack of gout. Between attacks, colchicine may be prescribed with good effect. The dosage is 0.5 mg. three times a day for three days a week. Cinchophen is often a useful antigout agent; 1.5 to 3 Gm. a day will promote the excretion of uric acid and lower the uric acid level of the blood. To guard against toxic hepatitis from this dosage the urine should be tested frequently for urobilinogen.

it must be found. If multiple food essentials are implicated, desensitization must often be resorted to and the essential nutrients restored to the diet.

The technic of discovering the food responsible for allergic symptoms varies with the clinical picture. When symptoms occur daily, the use of elimination diets is indicated. Rowe[16] and others have devised diets consisting of foods that are rarely responsible for allergy and yet are adequate in essential nutrients.

Diet 1	*Diet 2*	*Diet 3*
Rice Tapioca Rice bread	Corn Rye Corn pone Corn-rye muffin Rye Krisp	Tapioca White potato Breads made of any combination of soy, lima, potato starch, and tapioca flours
Lettuce Chard Spinach Carrot Sweet potato or yam	Beets Squash Asparagus Artichoke	Tomato Carrot Lima beans String beans Peas
Lamb	Chicken (not hens) Bacon	Beef Bacon
Lemon Grapefruit Pears	Pineapple Peach Apricot Prune	Lemon Grapefruit Peach Apricot
Cane sugar Sesame oil Olive oil Salt Gelatin, plain or flavored with lime or lemon	Cane or beet sugar Mazola Sesame oil Salt Gelatin, plain or flavored with pineapple	Cane sugar Sesame oil Soybean oil Salt Gelatin, plain or flavored with lime or lemon
Maple syrup or syrup made with cane sugar flavored with maple Royal baking powder Baking soda Cream of tartar Vanilla extract Lemon extract	Karo corn syrup White vinegar Royal baking powder Baking soda Cream of tartar Vanilla extract	Maple syrup or syrup made with cane sugar flavored with maple Royal baking powder Baking soda Cream of tartar Vanilla extract Lemon extract

The patient is given Diet No. 1 for ten to fourteen days. If the symptoms abate, other foods are gradually added to the diet or another diet is tried. If no relief is obtained, Diets No. 2 and No. 3 may be used. If none of the three diets ameliorate the allergic manifestations Rowe advocates the use of a simple milk diet. If this proves unsuccessful, food allergy is probably not responsible for the symptoms. Rowe has published numerous types of elimination diets for infants, for children, for the obese, for the diabetic, and for those suspected of sensitivity to fruits or vegetables.

If the symptoms of allergy are relatively infrequent and some food is thought to be the cause of them, a food diary may be useful in uncovering the allergenic agent.

The most frequent allergenic foods are milk, eggs, and wheat. The need for completely eliminating them from the diet depends on the severity of the symptoms. Moreover, patients allergic to ordinary cow's milk may not be sensitive to goat's milk, superheated milk, powdered or evaporated milk, or lactic-acid or peptonized milk mixtures. In mild cases, buttermilk does not cause symptoms of allergy. A soybean-milk formula adequate in calories, protein, calcium, phosphorus, and iron can often be substituted effectively for cow's milk.

The elimination of wheat as an allergen is seldom difficult. Wheat, however, is present in many foods and may be eaten unintentionally as thickening in soups, gravies, sauces, etc.

Eggs can be eliminated from the diet without great trouble. But the patient must beware of the "hidden" eggs in candies, cake, pastry, ice cream, souflées, and puddings.

CONVALESCENCE

The attention paid in recent years to the nutritional status of the convalescent patient has contributed notably to the reduction of morbidity and mortality rates in all branches of medicine. In surgery, proper preoperative and postoperative diet therapy is often second in importance only to the surgeon's skill.

PROTEINS

The recognition of protein as a sort of nutritional keystone is an important recent advance in medicine. Protein deficiency allows the fat content of the hepatic cell to increase, and this heightens the susceptibility of the liver to the damaging effects of anesthetics and toxins. Protein depletion is attended by a reduced capacity to produce antibodies and hence a reduced ability to combat infection.[24] Delayed fibroblastic proliferation interferes with the healing of wounds and bone injuries. Disruption of wounds, tissue edema, edema about suture lines, decubitus ulcers, delayed gastrointestinal motility, and malfunction or closure of a gastroenterostomy are among the postoperative sequelae of protein deficiency.

As a result of wounds, burns, infections, and surgical procedures, the nitrogen balance of the body becomes negative as the tissue protein is broken down. This has been attributed to the so called "toxic destruction of protein." A daily loss of 20 or 25 Gm. of nitrogen may be sustained for varying periods of time. If this follows the usual preoperative interval of dietary restriction, severe protein deficiency ensues. This causes pronounced loss of weight which prolongs convalescence, delays rehabilitation, and increases the possibility of complications.

A number of formulas for estimating the amount of protein required to make up a protein deficit have been published. For practical purposes it is enough to know that when no significant deficit is demonstrable, 2 or 3 Gm. of protein daily per Kg. of body weight will make up the usual loss that follows trauma or disease. When a deficit is demonstrable 3, 4 or even 5 Gm. of protein daily per Kg. is advisable.

It is not easy to overcome hypoproteinemia. It is often impossible to raise the protein level of the blood. The ordinary patient can be maintained in nitrogen equilibrium solely through the administration of protein hydrolysates; but the patient who has suffered shock as the result of an operation or severe infection may, within twenty-four hours, excrete all the nitrogen administered to him. It is of interest to note that normal dogs retain huge quantities of intravenously administered amino acids for brief periods but excrete them all within seventy-two hours.[8a]

Shorr[19] regards as insufficient the evidence that a slight reduction in the level of blood proteins is of importance in surgical patients and suggests that current efforts to make it up are excessive. While many will not agree with this viewpoint, it seems likely that the original enthusiasm for the indiscriminate administration of protein hydrolysates to all surgical and many medical patients will be tempered, in future, by evaluation of the necessity for such treatment. It has not been proved, for example, that a positive nitrogen balance is essential to normal postoperative recovery.

The administration of protein in most cases can usually wait until the patient is able to eat protein foods; to take protein in the normal way. A diet rich in meat, milk, eggs, cheese, and wheat will overcome protein deficiency more efficiently than artificially concentrated protein hydrolysates and concentrates and will, besides, supply essential food factors other than protein.* In this connection it may be observed that getting the patient on his feet as quickly as possible after an operation tends to accelerate the return of normal appetite: this will make him eat, which in turn will produce gain in weight. Rapid convalescence is likely to ensue.

The patient who, after an operation or at the beginning of disease, cannot tolerate solid food but can tolerate fluids, can easily be given the calories and the protein he needs by means of concentrated high-protein, low-fat drink consisting of skim milk to which are added skim-milk powder, protein hydrolysate or both, lactose, essential vitamin concentrates, and a drop or two of vanilla for flavor. A formula for oral or tube feeding is as follows:

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* For another viewpoint see Chapter 7. (*Editors.*)

HIGH-PROTEIN, LOW-FAT DRINK[*] FOR ORAL OR TUBE FEEDING

	Carbohydrate (Gm.)	*Protein* (Gm.)	*Fat* (Gm.)
6 whole eggs	—	36.0	36.0
2 egg whites	—	8.0	—
114 Gm. skim-milk powder	58.8	40.4	1.2
300 Gm. lactose (or beet cane sugar, or cerelose)	300.0	—	—
1000 Gm. skim milk	50.0	36.0	—
5 Gm. salt (when indicated)			
TOTAL	408.8	120.4	37.2

Total calories, 2446; total volume, about 1500 cc.

[*] After Varco. A very rich protein mixture can be prepared by adding 300 Gm. of skim-milk powder and 150 Gm. of protein hydrolysate to 3000 cc. of skim milk. This will furnish approximately 310 Gm. of protein.

A formula efficient in maintaining caloric and nitrogen balance when prolonged intravenous feeding is required follows:

INTRAVENOUS FEEDING FORMULA FOR MAINTENANCE OF CALORIE-NITROGEN BALANCE[*]

3000 cc. distilled water
300 Gm. dextrose
150 Gm. amigen
12.75 Gm. sodium chloride
2.0 Gm. potassium chloride
50 mg. vitamin C
75 mg. nicotinamide
5 mg. thiamin chloride
5 mg. riboflavin
5 mg. pyridoxine
2 mg. vitamin K
2 mg. calcium pantothenate

TOTAL CALORIES, 1774

[*] After Albright, from Barr, Conference on therapy. *Am. J. Med.* 3:474, 1947.

In surgical shock, or in hypoproteinemia following trauma, hemorrhage, or severe infectious disease, protein replacement is most effectively accomplished by the use of blood or plasma. A liter of plasma, for instance, supplies about 70 Gm. of protein. The high cost of plasma, however, the need for using it in quantity, its salt content, and the possibility that homologous serum jaundice may be transmitted by pooled preparations, may contraindicate its prolonged use in individual cases.

Fluid and Electrolytes

The need to maintain normal water and electrolyte balance during the course of disease and after surgery has long been recognized. Fluid requirements may be approximated as follows:

Uncomplicated cases

For vaporization (lungs, skin)	1000–1500 cc.
For urine	1000–1000 cc.
TOTAL REQUIREMENT	2000–2500 cc.

Complicated cases

(when patient has fever or hyperthyroidism,
or when weather is hot and humid):

For vaporization	2000–2000 cc.
For urine	1000–1500 cc.
TOTAL REQUIREMENT	3000–3500 cc.

If the patient is losing fluid through vomiting or diarrhea or via Wangensteen or biliary drainage, the fluids and the electrolytes lost must be replaced unit for unit to prevent dehydration and hypochloremia.

It is generally accepted that the average postoperative patient, requiring parenteral fluids and having essentially the same salt requirement as a normal subject, needs no more than a liter of normal saline solution every twenty-four hours; for the average adult ingests from 7 to 15 Gm. of sodium chloride a day, and a liter of saline solution contains 8.5 Gm. of sodium chloride. Recently, however, it has been pointed out that the administration of so much salt is usually in excess of body needs and may delay the recovery of the surgical patient. The rationale of withholding salt during the immediate postoperative period until the need for it is manifest has been substantiated by clinical and experimental observation. The use of more hypotonic solutions in parenteral therapy has been suggested as a more physiologic approach to the replacement of losses of fluid and electrolytes. The following criteria are useful in determining that adequate quantities of salt and water are being supplied:

1. Moist mucous membranes, normal skin turgor, absence of thirst;

2. Daily urine volume of 1000 cc. or more; specific gravity not over 1.020;
3. Absence of edema or pulmonary congestion;
4. Adequate urine salt excretion (definite precipitate when treated with silver nitrate).

Excessive loss of salt by sweating, vomiting, or Wangesteen or biliary drainage necessitates an increase in the total intake of sodium and chloride. In the complicated case, the level of the serum or plasma chlorides will indicate the degree of electrolyte depletion. Coller[4] advocates the following rule for approximating the necessary amount of salt replacement: for every 100 mg. that the blood chloride level must be raised, 0.5 Gm. of sodium chloride per Kg. of body weight should be administered.

When 1 liter of isotonic saline solution is being administered daily, the remaining fluid requirements are supplied as 5 per cent glucose in distilled water. If the salt requirements are high, from 2 to 5 per cent sodium chloride in water may be cautiously administered. Patients receiving parenteral fluids must always be observed carefully for evidence of edema, pulmonary congestion, hyperchloremia, and water intoxication —the results of overvigorous efforts to combat dehydration and hypochloremia.

A saline or distilled water solution of five per cent glucose supplies 4.1 calories per Gm. Thus 3000 cc. of 5 per cent glucose solution supplies about 615 calories. It is obvious that the caloric requirements of a postoperative patient can be satisfied only through the administration of additional glucose or, preferably, a well-rounded formula for intravenous feeding. The utilization of glucose increases as the quantities injected are increased. The object of glucose administration is not only to supply potential calories but also to increase the level of hepatic glycogen. The administration of insulin to the nondiabetic patient favors hepatic glycogenolysis and thus tends to defeat one of the purposes of the treatment. The use of insulin to "cover" glucose in the nondiabetic subject is therefore not recommended.

VITAMINS

After surgery, the patient's need for vitamins is increased about fivefold. Patients with complications, those who are undernourished, and those who are maintained for protracted periods with parenteral or tube feedings require generous amounts of all vitamins. The suggested dosages for supplementary parenteral feedings have been outlined elsewhere.

The importance of thiamine, niacin, and riboflavin in the maintenance of normal carbohydrate metabolism is well known. Administration of the whole vitamin B complex is advocated as the best protective dietary supplement. Vitamin C bears a direct relationship to wound healing. Since low levels of vitamin C are probably quite common, it may be assumed that all patients require supplementary ascorbic acid. The role of vitamin K in the clotting mechanism and its relationship to wound healing is important in surgery. In preparing patients for intestinal surgery it should be borne in mind that the administration of sulfonamide compounds may so reduce the bacterial flora of the bowel that bacterial synthesis of vitamin K may cease with resultant hypoprothrombinemia. In the presence of normal liver function, prompt return of the prothrombin level to normal follows the administration of vitamin K (menadione).

The Surgical Patient

In elective operations, surgery should be delayed until the patient's nutritional status is as sound as it can be made. The obese patient is a poor risk and should, if possible, be made to lose weight before an operation. If the patient is undernourished he should be given a diet rich in protein, high in calories, and supplemented with multivitamin concentrates. Anemia should always be corrected before surgery is undertaken.

The preoperative withholding of food is frequently overstressed. Preoperative fasting for twelve to eighteen hours is usually unnecessary. In elderly patients, in those with diabetes, and in the very young, hypoglycemia or acidosis or both may be the undesirable results of such starvation. Liquid nourishment should be given these patients five to six hours before they go to the operating room; or they may be fed parenterally at short intervals to insure that their stomachs will be empty. The average well-nourished patient can easily go without solid or semisolid food for twenty-four or forty-eight hours.

Ravdin and Zintel[15] advise withholding water after uncomplicated abdominal operations until active peristalsis is heard. Before that, they believe, fluids should be administered parenterally. When active peristalsis is heard, they permit small quantities of water and clear fluids such as tea and broth. The diet is then increased as tolerated by the patient to a full diet. It is no longer thought necessary to restrict all patients to liquid diet for two days, and then soft diet for another three days as a routine postoperative regimen.

Patients with complications or nutritional problems require special consideration. Many diets have been published in standard medical and surgical textbooks and in monographs on preoperative and postoperative care. Hospitals have routine liquid, soft, and house diets. The physician and surgeon should familiarize themselves with the regimens provided in their institutions and assess the diets carefully for adequacy in maintaining nutrition.

GERIATRICS

Nutrition as related to geriatrics can best be discussed under two aspects: (1) nutrition in the aging process; and (2) nutrition in the aged.

NUTRITION IN THE AGING PROCESS

Many variables determine length of life—heredity, climate, mode of living, sequelae of disease, and differences in the chemistry of the internal environment. Sherman[18] considers the latter fundamental and emphasizes the influence of nutritional factors. It is probable, he states, that "the chemistry of food influences aging more broadly and deeply than heretofore supposed."

Controlled data on the application of the newer knowledge of nutrition to longevity are not yet available, but some pertinent observations have been made of the influence on longevity of the dietary habits of certain tribes in India. According to McCarrison, the Hansa, who live chiefly on goat's milk, eggs, whole grains, and fruit, are vigorous and free from disease and survive to ages not attained by the members of other tribes who live chiefly on such nutritionally inferior foods as are cereals and legumes.

Some life-insurance statistics apply to the relation between nutrition and longevity.[20] These indicate that excess weight, which is usually due to eating more than the body can utilize profitably, reduces the life span significantly. Overweight of 25 per cent or more raises the mortality by 74 per cent above that of persons of normal weight. Insurance statistics show that underweight also shortens life.

Human experience in this respect is borne out by experimental studies with animals. McCay[11, 12] and others found, for example, that rats restricted in caloric intake but consuming a diet adequate in all essential food factors lived longer and retained their youthful appearance and vigor longer than rats allowed to fatten at will. But they also found that rats much below the average mean normal weight had short lives. The animals that lived longest were those of intermediate weight.

There is experimental evidence to show that a larger than normal proportion of protective foods in the diet will, like caloric restriction, increase the life span of animals and extend the period of health well into old age. Recent experiments by Sherman indicate that, in the protective foods, the nutrient factors that raise and prolong adult vitality in animals and postpone old age are vitamin A, calcium, and riboflavin.

Since, like childhood, growing old is a fundamental process, certain fundamental physiologic and anatomic changes must inevitably accompany it. These changes are essentially degenerative—dehydration and waste of tissue, tissue either not replaced at all or replaced with tissue of an inferior order. Long before such degenerative anatomic changes occur, however, functional disturbances may arise. In modifying the severity of both kinds of changes, nutrition plays an important part. It doubtless modifies basically, for example, the intracellular chemistry, which may help determine the very functional and structural alterations the geriatrist seeks to hold off.

It must be remembered, however, that to insure optimum health in the later years, optimum nutrition, in the broadest sense, must be applied long before the approach of those years, must be applied indeed, throughout life.

Nutrition in the Aged

There is no special diet for the aged, their diet should simply be a well-balanced one abounding in protective foods. Certain factors, however, which often militate against this difficulty should be eliminated. These factors are the following:

FAULTY FOOD HABITS

The old frequently become food faddists and avoid foods containing essential nutrients.

IMPROPER DENTURES

These may cause painful ulcers in the mouth and interfere with proper chewing. As a result, the old may limit themselves to plain starchy foods lacking in vitamins and minerals.

DECLINE OF THE SENSE OF TASTE

This reduces appetite, without which there is little incentive for eating a great variety of food. The food selected for the diet of the old should therefore be attractively prepared and served, even though puréed. Attention should be given to the consistency of the food, the size and frequency of meals, and the food tradition of the individual.

DISTURBANCE IN THE FUNCTIONING OF THE GASTROINTESTINAL TRACT

Digestion in the old is not so efficient as in the young. Gastrointestinal function, for example, often slows down. The salivary secretion is reduced, as is its ptyalin content. Further, the hydrochloric acid and pepsin in the gastric secretion are greatly reduced; achlorhydria has been reported in a substantial proportion of the aged—from 23.9 to 65 per cent. The external pancreatic ferments, especially lipase, are also diminished. Gastric emptying time, however, is not altered in the aged.

The dietary management of the aged may be based upon the following considerations.

CALORIES

The old should avoid both overweight and underweight. They should eat enough to maintain normal weight. But owing to their reduced physical activity and the slowing of their metabolic processes, reduction of their caloric intake is desirable. Of the two extremes, underweight is to be preferred to overweight, since the latter is the more likely to be accompanied by diabetes mellitus, hypertension and degenerative vascular disease.

PROTEIN

Many older persons suffer from hypoproteinemia. This may manifest itself clinically as fatigue, secondary anemia, edema, or lowered resistance to infections. The hypoproteinemia may be due to reluctance to eat meat because of the false notion that meat damages the kidneys or raises the blood pressure, or it may be due to difficulty in chewing owing to poor dentures or want of sufficient teeth.

Old people should consume 1 Gm. of protein daily per Kg. of body weight. They can get this amount from fish, flesh, or fowl (minced, scraped, or flaked), liver, visceral organs, milk, cheese, ice cream, eggs, and cereal-germ products.

CARBOHYDRATE

Although the old obtain most of their nourishment from carbohydrate, too much carbohydrate is harmful to them; for it may be converted into fat and lead to obesity, or tax the insulogenic mechanism and lead to hyperglycemia and glycosuria. It should be remembered, too, that the richer the diet is in carbohydrate, the higher the requirement of vitamin B complex.

The old can be supplied their carbohydrate in the form of oatmeal, whole wheat or vitamin-enriched bread, fruit and fruit juices, and vegetables, especially the green and yellow ones. Among vegetables, kale, dandelion, and turnip greens are preferred to spinach, beet greens, and rhubarb, since the latter contain greater amounts of oxalic acid, a calcium binder. The vegetables served to the old should be cooked soft or put through a sieve. Cooked cereals and mashed potatoes are good sources of carbohydrate for the old.

FAT

For obvious reasons the old should avoid a diet rich in fat or fried food. Fat is more liable to cause distress than protein or carbohydrate; a fatty diet is likely to lead to obesity; and a high-cholesterol diet may be an important contributory cause of coronary artery disease. Enough fat should be eaten, however, to maintain body weight.

VITAMINS

If the diet is adequate in all respects and abounding in protective foods, there should be no danger of vitamin deficiency. In certain conditions, however, supplementary vitamins are necessary to effect relief from pathologic manifestations of old age. Geriatric patients with such chronic disorders as arteriosclerotic heart disease, liver dysfunction, and disease of the gastrointestinal tract are likely to show signs of nutritional deficiency as a result of either inadequate absorption or inadequate utilization of vitamins. The old who lack satisfactory teeth, either natural or artificial, may subsist on an inadequate diet and consequently develop symptoms of vitamin deficiency. There is laboratory evidence (Rafsky and Newman)[14] that apparently normal old people may have low blood levels of ascorbic acid, thiamine, carotene, and vitamin A. In these conditions supplementary vitamins are clearly indicated. Some manifestations of vitamin deficiency in the old—dry itching of the skin, for example—often clear up considerably after prolonged administration of large doses of vitamin A.

MINERALS

Iron and calcium are perhaps the minerals needed most by old people. A mild anemia due to deficiency of iron, for instance, is frequently found in the old. To prevent this, foods rich in iron—lean meats, liver, eggs, whole wheat, leafy vegetables, molasses, raisins, and peaches—should be included in the diet. These foods are particularly desirable because they contain also traces of copper, manganese, and cobalt, minerals that enhance the synthesis of iron into hemoglobin.

Demineralization of the bones is frequent among the old. And although it is often impossible to recalcify aged bones, it is not impossible to help prevent decalcification of the bones of the sort often seen in the aged poor. This, however, requires an adequate supply of dietary calcium all through life.

The maintenance of a normal calcium level in the blood is necessary also to preserve the optimal irritability and elasticity of the nervous and muscular systems, regulate normal blood clotting, and help maintain the acid-base economy of the body. Old people should therefore drink a pint of milk daily, or eat plenty of cheese or leafy green vegetables, or get calcium in some pharmaceutical preparation.

LIQUIDS

The old need a liberal fluid intake. It may be taken in the form of milk, plain water, carbonated water, tea, coffee, or cocoa. Alcohol in moderation is an excellent food and drink for the elderly.

SUMMARY

The old should (1) get enough calories to maintain normal weight for age, sex, and height; (2) get a gram of protein a day for every kilogram of body weight; (3) use fats sparingly; (4) let carbohydrate supply most of the food requirement; and (5) eat plenty of foods rich in vitamins and minerals. In certain instances, supplementary vitamins may be necessary.

The following dietary is recommended by Sebrell[17] for the basic needs of the old:

> One pint of milk or its equivalent. Part of this may be utilized in creamed soups, puddings, milk toast, etc.
> One serving of orange, grapefruit, tomatoes, or their juices. Raw cabbage or salad greens may be substituted if desired, provided no alimentary contraindications exist.
> One serving of green or yellow vegetables, some raw.
> One serving of potatoes or other vegetable or fruit.
> One serving of whole grain cereal, oatmeal or wheat.
> One egg daily, or at least three or four a week.
> One serving of meat, poultry, sea food, or other protein-rich food.
> All bread and flour should be enriched or whole grain.
> Butter, margarine, fortified with vitamin A, peanut butter, or other vitamin-rich fats as indicated.

PREGNANCY

Pregnancy is a period of nutritional stress, for the pregnant woman must consume adequate nutritive materials both for herself and for the developing fetus. Since her basal metabolic rate rises in the latter months of pregnancy, there is then a consequent increase in the requirement of calories, protein, minerals and vitamins.

Latent deficiency disease may become overt in pregnancy just as it may in the course of disease or after traumas and surgical procedures. In an analysis of the diets of 514 pregnant women, Williams and Fralin[23] classified only 10 of the diets as good; 209 were fair and 295 poor. This is tragic; for it has been demonstrated[2, 3] that women properly nourished during pregnancy are less liable to the complications of pregnancy, less likely to have miscarriages, and less likely to bear dead or premature babies.

The following general guide should insure adequate nutrition during pregnancy:*

Whole milk	One liter
Lean meat	At least one liberal serving (115 Gm.); liver is desirable at least once each week
Egg	At least one
Fruit	Two or more servings (1 to 1½ cups, 200–300 Gm.) Two medium oranges or unstrained orange juice (225 Gm.) or its equivalent should be taken each day
Vegetables	Two or more servings of cooked or raw vegetables (1 to 1½ cups, 200–300 Gm.) these should include dark green leafy or deep yellow vegetables, also legumes several times each week; in addition a medium potato (150 Gm.) cooked in the skin should be eaten daily
Bread and cereal	Whole grain or enriched bread at least four slices daily (½ cup cereal is equivalent to 1 slice of bread)
Butter or fortified margarine	30 ml.
Additional foods	Consisting of either more of the foods already listed or other foods of one's own choice, adjusted to individual energy needs and in relation to desired weight gain
Vitamin D	Some form of vitamin D to supply 400–800 I.U.

PROTEIN

There is ample evidence that the protein intake of pregnant women in the United States and Canada, where today probably the highest living standards in the world obtain, is often grossly inadequate. Protein supplies the amino acids necessary for the formation and replacement of maternal and fetal tissue and the production of breast milk. It is well established that the greater the retention of nitrogen in the latter half of pregnancy, the better the outlook for a good supply of milk. A relationship between low protein intake and the incidence of toxemia of

* Adopted from Burke, B. S., and Kirkwood, S. B.

pregnancy has been suggested, but is still debatable; however available evidence suggests that toxemia of pregnancy is more common among malnourished women. Deficiencies in the protein content of the diet, however, may lead to hypoalbuminemia, lowering of the colloid osmotic pressure, and edema. It has been demonstrated that an adequate protein intake facilitates the absorption of calcium and prevents the development of the macrocytic anemia of pregnancy.

Nitrogen storage produced by a positive nitrogen balance begins as early as the tenth week of gestation, and a gain of 200 to 400 Gm. of nitrogen may occur during pregnancy. In the puerperium, negative nitrogen balance ensues. This is probably due to uterine and pelvic involution and to lactation.

It is obvious that the gravid patient requires a liberal supply of protein. The National Research Council has recommended 85 Gm. a day, or about 1.5 Gm. per Kg. of body weight, for the average pregnant woman; and 100 Gm. a day for the lactating woman. About two-thirds of this protein intake should be derived from animal sources. Where the previous nutritional status has been poor these requirements must be increased.

Calories

The caloric requirements of the pregnant woman are above usual levels after the first trimester. Carbohydrates should supply 50 or 60 per cent of the calories, and fat 30 or 35 per cent. The caloric intake must be adjusted to prevent a weight gain greater than the 9 or 11 Kg. considered to be normal. Caloric restriction to prevent excess gain in weight requires adjustment of the diet so as not to interfere with the intake of essential proteins, minerals and vitamins. Obesity has been associated with both toxemia of pregnancy and complications at parturition.

Minerals

The pregnant woman requires calcium to supply the demands of the fetus as well as for the production of milk. Calcium deposition and absorption in bone are continuous processes and equilibrate one another in the normal organism. Since calcium is drained from the mother's skeleton during pregnancy, an augmented intake is necessary to maintain the equilibrium. The teeth participate only slightly or not at all as a source of calcium during pregnancy; calcium drain from the teeth, therefore, does not explain the dental decay of pregnancy. An inadequate intake of calcium may result in maternal osteomalacia, impaired lactation, fetal rickets, and perhaps defective deciduous tooth formation, though the latter has been more specifically related to the protein intake.

The calcium requirement of the pregnant woman is about double that of the nonpregnant one. About 1.5 Gm. of calcium daily during pregnancy, and 2.0 Gm. daily during lactation, are recommended. A good diet supplemented with a liter of milk a day will supply enough calcium during pregnancy; one and a half liters of milk a day are required during lactation. The phosphorus requirement will be amply met if the calcium requirement is provided from dietary sources.

Pregnancy raises the requirement of iron, not only to supply both maternal and fetal needs but also to prevent the development of an iron-deficiency anemia. Iron is an essential component of hemoglobin molecules for oxygen transport and of respiratory enzymes for cellular oxidation. The gravid female provides 0.5 Gm. of iron to the full-term fetus. The National Research Council has recommended 15 mg. of iron daily during the latter half of pregnancy. Two-thirds of this requirement will be insured by providing a diet including one serving of meat, one egg, 500 ml. of milk, 4 slices of whole wheat or enriched bread, and 2 servings of vegetables. One hundred grams of liver contains 8 mg. of iron. The daily administration of 0.3 Gm. of iron (as ferrous sulphate, ferrous gluconate, etc.) is recommended as a supplementary supply if a hypochromic anemia exists.

VITAMINS

Experimental studies[21, 22] have established the fact that certain congenital malformations are produced in the offspring of rats when the maternal diet is deficient in vitamin A and riboflavin. The malformations have a characteristic pattern. Those resulting from deficiency of vitamin A in the maternal diet included blindness, accessory ears, cleft palate, harelip, subcutaneous cysts, misplaced kidneys, and abnormal eye structures. Developmental defects in the offspring of female rats fed a diet deficient in riboflavin were found by Warkany and his associates to be of five general types: shortening of the mandible, deformities of the extremities, fusion of ribs, cleft palate, and occasionally malformations of the soft tissues. An etiologic relationship in humans between maternal dietary deficiencies and congenital malformations of the newborn is not implied by these studies.

VITAMIN B_1

Deficiency of thiamine may manifest itself in pregnancy as polyneuropathy, anorexia, alteration in cardiac function, loss of skeletal and smooth muscle tone, or loss of weight. Approximately 1.5 mg. a day is the recommended requirement of thiamine in pregnancy.

VITAMIN C

There is a marked increase in the need for vitamin C during the latter half of pregnancy. The National Research Council has recommended a daily intake of 100 mg. of ascorbic acid. This can be supplied by 225 gm. of orange juice.

VITAMIN D

Vitamin D is essential for the absorption of both calcium and phosphorus from the small intestine. It is essential to adequate nutrition especially during pregnancy and lactation, when the demand for calcium is high. For the latter half of pregnancy and for lactation, the National Research Council has recommended 400 to 800 I.U. of vitamin D daily.

VITAMIN K

The administration of vitamin K to the mother in labor has been efficacious in preventing neonatal hemorrhage.

The dietary allowances recommended for pregnant and lactating women by the Food and Nutrition Board of the National Research Council are shown in Appendix Table A.

BIBLIOGRAPHY

1. Allen, F. M. Arterial hypertension. *J.A.M.A.* 74:652, 1920.
2. Burke, B. S. Need for better nutrition during pregnancy and lactation. *J. Am. Dietet. Assn.* 17:102, 1941.
3. Burke, B. S., Stuart, H. C. Nutritional requirements during pregnancy and lactation. *J.A.M.A.* 137:119, 1948.
4. Coller, F. A., and Maddock, W. G. Water and electrolyte balance. *Surg. Gynec. & Obstet.* 70:340, 1940.
5. DuBois, E., and Sodestrom: quoted by DuBois, E. Basal Metabolism in Health and Disease. Philadelphia, Lea, 1936.
6. Ebbs, J. H., Tisdall, F. F., and Scott, W. A. Influence of prenatal diet on mother and child. *J. Nutrition* 22:515, 1941.
7. Kempner, W. Treatment of kidney disease and hypertensive vascular disease with rice diet. *North Carolina M. J.* 5:273, 1944.
8. Leary, T. Genesis of atherosclerosis. *Arch. Path.* 32:507, 1941.

8a. Levine, R., and Schneeberg, N. G. *Fed. Proc.* March, 1948.

9. Lukens, F. D. W. Diagnosis of treatment of disorders of adrenal glands. *M. Clin. North America* 26:1803, 1942.
10. McCarrison, R., in Rose, M. S. *Feeding the Family.* New York, Macmillan, (Ed. 4), 1940.
11. McCay, C. M., Maynard, L. A., Sperling, Gladys, and Osgood, H. S. Nutritional requirements during the latter half of life. *J. Nutrition* 21:45, 1941.

12. McCay, C. M. Diet and aging. *J. Am. Dietet. Assn.* 17:540, 1941.
13. Proger, S. H., and Magendantz, H. Diet in treatment of heart disease. *Internat. Clin.* 2:62, 1936.
14. Rafsky, H. A., and Newman, B. Nutritional aspects of aging. *Geriatrics* 2:101, 1947.
15. Ravdin, I. S., and Zintel, H. A., in Wohl, M. G. (ed.) *Dietotherapy.* Philadelphia, Saunders, 1945, p. 845.
16. Rowe, A. H. "Nutrition in the allergies" in Wohl, M. G. (ed.) *Dietotherapy.* Philadelphia, Saunders, 1945.
17. Sebrell, W. H. "Nutritional Problem" in Stieglitz, E. J. *Geriatric Medicine.* Philadelphia, Saunders, 1943.
18. Sherman, H. C. Some relations of food chemistry to the time of aging and the length of life. News Edition, *J. Am. Chem. Soc.* 19:1081, 1941.
19. Shorr, E. Discussion, Conference on Therapy: The use of protein hydrolysates. *Am. J. Med.* 3:472, 1947.
20. Stieglitz, E. J. The Second Forty Years. Philadelphia, Lippincott, 1946.
21. Warkany, J., and Schraffenberger, E. Congenital malformations induced in rats by maternal nutritional deficiency. The Preventive Factor. *J. Nutrition* 27:477, 1944.
22. Warkany, J., and Schraffenberger, E. Congenital malformations induced in rats by maternal vitamin A deficiency: defects of eye. *Arch. Ophth.* 35:150, 1946.
23. Williams, P. F., and Fralin, F. G. Nutrition study in pregnancy: Dietary analyses of 7 day food intake records of 514 pregnant women, comparison of actual food intakes with variously stated requirements, and relationship of food intake to various obstetric factors. *Am. J. Obst. & Gynec.* 43:1, 1942.
24. Wohl, M. G., Reinhold, J. G., and Rose, S. B. Antibody response in patients with hypoproteinemia with special reference to the effect of protein or protein hydrolysate supplementation. *Arch. Int. Med.* 83:402, 1949.

Chapter 28

OBESITY

L. H. Newburgh

OBESITY is that condition in which the body contains an abnormally large amount of adipose tissue. The excessive fat may be evenly distributed or may be present to a much greater extent in some regions than in others. When the accumulation is sharply localized to one or more discrete encapsulated masses, one speaks of "lipomatosis" in contradistinction to "obesity."

Fisk[17] has shown that the average weights of persons over 30 years of age are too great as judged by life expectancy and has found that the average weight at the age of 30 is the most desirable weight for the remainder of life. Appendix Tables E and F, are based on that principle. The heights include shoes, and the weights include clothes, and food.

Dublin and Lotka[14] have analyzed the influence of weight on the duration of life of 192,304 men aged 21 years or over when accepted for life insurance. The deaths per hundred thousand, age being disregarded, are given in Table 34.

The investigators concluded that "the penalty of overweight is one-fourth to three-fourths excess in mortality." These studies become still more informative when related to age, since excessive weight carries a much greater risk beyond 45 years of age than earlier (Table 35). Fisk found likewise that persons in full middle life who weigh 20 lb. (9 Kg.) more than the average instead of 10 lb. (4.5 Kg.) less are incurring an extra 25 per cent risk.

TABLE 34. INFLUENCE OF WEIGHT ON MORTALITY

DEATHS PER 100,000 MEN ACCEPTED FOR INSURANCE

Weight	*Deaths*
Standard	844
Underweight, total	848
Overweight, total	1111
Underweight, 5–14%	833
Underweight, 15–34%	913
Overweight, 5–14%	1027
Overweight, 15–24%	1215
Overweight, 25% or more	1472

TABLE 35. INFLUENCE OF WEIGHT ON MORTALITY AS MODIFIED BY AGE

DEATHS PER 100,000

	Age in years	
Weight	Under 45	Over 45
Standard	463	1308
Underweight, total	498	1274
Overweight, total	527	1824

ETIOLOGY

IS THERE A DISORDER OF THE UTILIZATION OF ENERGY?

Because of the prevalence of the belief that some patients gain weight even though they do not overeat and that others do not lose when they are underfed, there has been a continued search for some metabolic aberration in this disease.

BASAL METABOLISM

Early students found that, pound for pound, obese persons produce less heat in the resting postabsorptive state than do normal controls. Had they made the comparison on the basis of height, they would have found that the heat production of obese persons was greater than normal. But Rubner, Lusk, and others have demonstrated that the basal heat production of all mammals is proportional to the surface area of the body and that no such relation exists when either weight or height alone is used as the basis of comparison.

Subsequently, Boothby, and Sandiford[8] measured basal heat production in 94 obese patients and found that in 81 per cent of them the rates were within 10 per cent of the normal heat production per square meter. In 3 instances the rates fell between −16 and −20 per cent, and another patient produced heat at a rate more than 16 per cent above normal.

Strouse, Wang, and Dye[49] compared the basal metabolic rates of normal persons with those of underweight and of overweight subjects. Per square meter of body surface they found practically no differences.

Among 180 cases of extreme obesity Grafe[22] found only 3 in which there was a definite decrease in basal metabolic rate.

The occasional moderately low rate (from −15 to −25 per cent) exhibited by an obese person does not contribute to the understanding of obesity, since equally low rates are encountered as frequently among healthy persons.

TABLE 36. TOTAL BASAL HEAT PRODUCTION (CALORIES)

FIVE OBESE WOMEN COMPARED WITH IDEAL VALUES

	Weight lb.	*Surface Area* sq. M.	*Calories sq. M./Hr.*	*Total No. of Calories/Hr.*
Ideal	129	1.59	36.5	58
Observed	238	2.06	35.5	73

The few obese persons whose basal metabolic rate is low enough to be definitely pathologic will be found to be suffering from some disease in which adiposity is a complication or an unrelated accompaniment and not the primary abnormality.

These and many other studies lend overwhelming support to the statement that obesity is not caused by lessened expenditure of energy in the basal state. In fact, an obese person produces more heat than a normal person of corresponding age, height, and sex. While both will produce the same number of calories per square meter of body surface per unit of time, the obese person has a larger surface, and therefore the total heat produced by the obese person in the basal state is greater actually than the total basal heat produced by the normal person.

Strang and Evans[46] made careful measurements of the basal metabolic rates of 5 obese women, and the average values are compared in Table 36 with the predictions for a normal woman of the same average age.

In order to emphasize the large expenditure of energy of an obese person in the basal state the authors gave the following hypothetic example: An obese woman aged 49, 5 feet (152 cm.) tall, weighs 294 lb. (133 Kg.). Her surface area accordingly will be 2.2 square meters. Her basal heat production will be 77 calories per hour. In order to produce the same amount of heat in the basal state, a normal man of the same age would have to be 6 feet 1 inch (185 cm.) tall.

Specific Dynamic Effect

If the heat production of a person who has been without food for twenty hours and has been reclining quietly and comfortably for a half hour (basal state) is carefully measured and he is then fed, he will shortly produce more heat per unit of time than he did in the fasting state. This response is not caused by digestion or absorption, since it is equally great after the intravenous injection of dextrose or some of the amino acids that result from the digestion of protein. If some metabolic fault prevented or greatly lessened this specific response to food, the person so afflicted would gain weight, provided he continued to partake of the same amount and the same kind of food and provided he did not increase his activity. His appetite however, might direct him to eat less, since he needed less, and in that case his weight would not increase. Several students have attributed obesity to lessened specific dynamic effect of food, without making any allowance for the second alternative.

Many attempts have been made to show that the caloric response to food is controlled by the hypophysis. Thus Plaut[38] stated, as a result of her studies, that a normal basal metabolic rate, coupled with a lowered specific dynamic response to protein, is characteristic of disease of the hypophysis. Using these criteria, she expressed the belief[39] that she was able to show that in certain cases obesity was caused by hypofunction of the pituitary. Kestner, Knipping, and Liebesny subsequently published many determinations that seemed to confirm her work. The technic employed by these investigators has been criticized by a number of workers. Dürr,[15] for example, pointed out that a normal person exhibited no response to food in three hours and a response of only 18 per cent in five hours. Lauter[29] in careful studies found that the specific dynamic response of normal subjects varies so widely that only its total absence is of diagnostic significance. Gaebler,[21] working in Lusk's laboratory, found that dogs from which the hypophysis had been removed responded normally to a standard protein meal.

Because of the disagreement, Johnston[28] reinvestigated this question. She restricted her studies to patients in whom destructive diseases of the pituitary were demonstrated, usually by operation or at autopsy. She obtained large responses in all cases (18 to 28 per cent) and pointed out that it was not possible to secure uniform results in human beings. She found it impossible to obtain a consistent response to sucrose or amino-acetic acid in a normal subject maintained on a constant diet. This again emphasized the caution with which small responses must be interpreted.

Later work suggests that the liver is responsible for the increased heat liberated during the metabolism of protein. Bollman and Magath[7] showed that deaminization took place in the liver, and Wilhelmj and Mann[53] later found that administration of amino acids to hepatectomized dogs did not increase the heat production. Finally, Dock,[13] by excluding various portions of the bodies of rats from the circulation, found that at least 85 per cent of the specific dynamic heat was liberated in the abdominal viscera.

TABLE 37. SPECIFIC DYNAMIC EFFECT OF FOOD

Type of subject	*Individual variation no. of calories*	*Average no. of calories*
Normal	43 to 61	51
Obese	44 to 74	58
Thin	59 to 78	67

The relation of the specific dynamic effect to the obese state has been studied so painstakingly and comprehensively by Strang and McClugage[47] that their results may be accepted with great confidence. They emphasized that the base line, that is, the value of the basal metabolism, is the most important feature of the test. Earlier workers have failed to train their subjects sufficiently. Strang and McClugage have repeated basal determinations until uniform results were obtained.

These workers emphasized the irregularity of the response to food when viewed from hour to hour and were in agreement with Benedict and Carpenter[4] that a true appreciation of the thermal effect of a meal is obtained by focusing the attention on the total increment.

With these considerations in mind, they studied 5 normal, 5 thin, and 8 obese persons. The total increment for the eight hours following the ingestion of the test meal will be found in Table 37.

These studies have been described in considerable detail with the hope of convincing the reader that the acquisition of adiposity cannot be attributed to a lessened specific dynamic effect of food.

LUXUSKONSUMPTION

Grafe and Graham[23] have maintained that in addition to the specific dynamic response, which comes to an end in twelve hours or less, the heat production of the organism throughout the twenty-four hours is influenced by the quantity of food eaten. Leaving out of consideration the increases that accompany activity and the specific dynamic effect, they expressed the belief that the intensity of the metabolism is stimulated by generous (excessive) feeding and depressed by meager supplies of food. Such a mechanism would tend to maintain constancy of weight. Obesity would develop when the mechanism failed to respond to overeating, and leanness would be the result of abnormally great responses.

Grafe expressed the belief that he had demonstrated the existence of this mechanism by recording the heat production in the resting-fasting state following various types of feeding. He thus set aside the classic experiments of Rubner, Lusk, Benedict, and many others, who have shown that all mammals produce heat at approximately the same rate per square meter of body surface when they are in the basal state. However, many thousands of determinations have proved that the basal heat production per square meter per hour by a normal person can be predicted with great accuracy without any knowledge of what he has been eating during the preceding days.

It has also been well established that the basal oxidative rate is greatly depressed by prolonged, severe underfeeding. Zuntz,[55] for example, showed that the decrease might amount to as much as 30 per cent of the normal value. The organism does, then, possess a mechanism that retards the destruction of body tissues when it has to contend with starvation. But this phenomenon seems to bear no relation to Grafe's concept that the lean organism is so because it overoxidizes an otherwise adequate supply of food or that adiposity represents underoxidation.

Grafe and Koch[24] reported a study on a patient whose normal weight was 62.6 Kg. and whose height was 156 cm. Because of stenosis of the pylorus accompanied by persistent vomiting, his weight had fallen to 40 Kg. In this emaciated condition he produced 30 calories per square meter per hour in the resting-fasting state. Relief of the stenosis and subsequent feeding of 100 calories per kilogram brought his weight up to 60 Kg. He then produced 40.7 calories per square meter, which was within 3 per cent of the prediction for a man of his age and height and of normal weight. This study merely confirmed Schöndorff's[41] earlier work that starvation depressed the basal metabolism. Grafe did not present any data to support his contention that continued superalimentation was capable of causing the oxidations to proceed at a rate greater than normal.

In order to test Grafe's postulate, Wiley and Newburgh studied the responses of a thin person by means of a method* developed by them for determining the total heat production for any desired length of time.

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* This method is described in the section dealing with the total metabolism of obese persons.

The subject was 28 years old, 6 feet (183 cm.) tall, and weighed 45 pounds (20 Kg.) less than normal. For the first eighteen days he was fed a constant diet that yielded 2922 calories daily. During this same period the twenty-four-hour heat production averaged 2947 calories. His weight at the beginning was 57,562 Gm., and at the end it was 57,548 Gm. He was then fed a diet that yielded 4755 calories daily. This was an increase of 1833 calories. During the fifteen days the latter diet was taken the subject gained 4410 Gm. (nearly 10 lb.). Heat production per twenty-four hours in the second period averaged 3082 calories. Accordingly, he produced 135 more calories when he was ingesting about 5000 calories than when he took about 3000 calories, an increase of 4.5 per cent in total metabolism.

The increase in the surface area that accompanied the increase in weight accounted for 68 extra calories and the additional carbohydrates and fat could be expected to increase the specific dynamic effect of the second diet by 85 calories, according to a calculation by Lusk.[31] Accordingly, the predicted increase in heat production during the second period without recourse to *Luxuskonsumption* is 153 calories, whereas the actual increase was only 135 calories. When the subject was partaking of the smaller diet, the fasting-resting heat production was at the rate of 35.5 calories per square meter per hour. At the end of the period of overfeeding he produced 36.9 calories under the same conditions. The difference of 1.4 calories is not significant. There was, then, no evidence that either the basal or the total metabolism was stimulated by superalimentation.

TOTAL METABOLISM

It has repeatedly been observed that some obese patients who are receiving only minimal quantities of food fail to lose weight. Van Noorden[37] reported such experiences many years ago. More recently Grafe[22] has published several striking examples, one of which is reproduced here in part.

The patient, aged 38, was 5 feet, 4 inches (163 cm.) tall and weighed 378 lb. (171 Kg.). She became stout at 10 years of age. When she was 20 years old, she weighed 176 lb. (80 Kg.). She married at this time. Subsequently, she gave birth to four babies and gained weight after each delivery. When first seen by Grafe she exhibited enormous adiposity of the trunk, legs, and upper arms. During the first month of treatment she lost 30 lb. (14 Kg.). Then without change in treatment the loss of weight gradually diminished, and finally for two weeks there was no loss at all. The weight remained stationary at 341 lb. (155 Kg.). During these two weeks her diet contained 647 calories, and the basal metabolism was 2000 calories. Grafe calculated that the daily caloric deficit was about 2000. In addition to the restricted diet her fluid intake was limited to about 500 cc. daily. Under these circumstances the body should have lost 8.5 lb. (4 Kg.) of adipose tissue during these two weeks. Even though the patient received four injections of mersalyl solution and 3 to 8 mg. of thyroxin daily, the volume of urine was small, averaging 500 cc. daily. She continued the treatment at home in a little milder form and lost 13 lb. (6 Kg.) in the next few weeks.

This capacity to resist loss of weight in spite of the most rigorous treatment has given rise to much speculation and confusion. To many physicians it has seemed useless or even cruel to continue to underfeed patients of this type, since they seemed to be doomed to hopeless adiposity.

Such paradoxic conduct might arise from some obscure metabolic abnormality that permits conservation in the utilization of energy. In that case, the total heat production would be strikingly less than normal. But no measurement of the twenty-four-hour expenditure of energy had been published prior to our reports. Such patients might have been studied in a respiration chamber for one or possibly a few consecutive days. But the restricted activity and short intervals of time imposed by the chamber made that method of doubtful value for this special purpose. We accordingly investigated the feasibility of calculating the dissipation of energy for any desired length of time and without curtailment of activity from the insensible loss of weight, since Benedict and Root[5] had shown that there is a quantitative relation between the hourly insensible loss and the basal metabolism.

The method[35] is based on the following considerations: It is well known that evaporation of water from the skin and lungs is one of the mechanisms by which the body rids itself of heat. This portion of the outgoing heat is removed at the rate of 0.58 of a large calorie per gram of water vaporized. If an accurate procedure can be devised for the calculation of the weight of the water vapor and if the organism loses a fixed percentage of the heat of its metabolism by vaporization of water under a wide variety of conditions, a method will be at hand for measuring the total heat production day after day.

To determine whether a fixed percentage of the total heat was removed through vaporization during consecutive twenty-four–hour periods by men and women who continued to lead their usual lives, we proceeded as follows (Table 38, first group): The subjects were asked to adjust their clothing to avoid conscious discomfort from heat and cold and to forego strenuous exercise such as handball. The experiments were conducted during the winter months. The subjects spent most of their waking hours in buildings heated to the usual temperature, and each of them was out of doors several times each day for a few minutes at a time. They all slept with the windows of the bedroom open. Two of the subjects were diabetic. The remainder of the group were normal young men and women busily occupied with care of patients or with work in a laboratory. The weight of each person, nude and in the fasting state, was recorded each morning at the same time on a balance sensitive to 1 Gm. The prescribed diet was prepared and weighed in the special diet kitchen of the hospital. The food used varied from day to day. The weights of the urine and the stool were determined each twenty-four hours.

These experiments were based on the following concepts: A well-nourished adult who is following a routine of life and who is fed a fixed diet, the calorific value of which approaches his maintenance requirement, will shortly establish nitrogen balance. In addition, the glycogen store in the liver will come into balance with the carbohydrate of the diet. Thereafter, the person will oxidize carbohydrate in the amount supplied by the diet provided the time interval under consideration is not too brief. It was not expected that this principle would hold for each cycle of twenty-four hours, but that the subject would be in carbohydrate balance if each period lasted one week. Under these circumstances, change in body weight could be attributed to deposition or loss of adipose tissue, provided the observations of any subject were continued for several weeks. When the record was completed, the average daily metabolic mixture would correspond with the diet except that any change in body weight over the whole period would have to be reduced to a daily average and then 90 per cent of it either added to or subtracted from the dietary fat.* The calories of the diet thus corrected were taken to be the daily heat production of the subject.

TABLE 38. AVERAGE PERCENTAGE OF TOTAL HEAT LOST BY EVAPORATION OF WATER

Subject	*Period* days	*Age* yr.	*Sex*	*Heat lost by evaporation of water* %	*Comment*
			FIRST GROUP		
1	72	56	M	23.8	Diabetic patient
2	5	30	M	24.2	Diabetic patient
3	18	28	M	24.2	Chemist
4	44	24	F	24.4	Chemist
5	35	25	M	24.1	Medical student
6	68	23	M	24.7	Graduate student
7	72	24	M	25.2	Graduate student
			SECOND GROUP		
8	145	24	M	24.2	Student
9	30	18	M	24.3	Patient in bed
10	30	15	M	24.8	Patient in bed
11	30	18	M	24.8	Patient in bed
12	25	47	M	24.7	Patient in bed

---

* Since adipose tissue contains 10 per cent water and dietary fat is expressed in anhydrous terms, 90 per cent of the change in weight is used.

Having arrived at the metabolic mixture we could calculate the production of carbon dioxide and the absorption of oxygen. Since the insensible loss of weight had been determined for each twenty-four hours, the weight of the insensible water could be derived by means of the equation

$$I.W. = I.L. - (CO_2 - O_2)$$

When the insensible water is known, the heat removed by it is simply $I.W. \times 0.58$. From this value and the amount of heat production, the percentage of heat removed by the vaporization of water was calculated by means of the expression

$$\frac{I.W. \times 0.58}{heat\ production}$$

However, in the case of the 2 diabetic subjects it was not necessary to use a circuitous method to arrive at the materials oxidized, since both had been living on carefully prescribed, weighed diets for years and had long since come into balance.

Table 38 shows the average percentage of the total heat lost through evaporation of water by each subject.

The first group of 7 adult persons, whose lives were restricted only in the few important ways noted, showed a striking tendency to rid themselves of the same proportion of the heat of their metabolism by vaporization of water.

To obtain greater accuracy when the second group of subjects was studied, the nitrogen exchange was actually determined and the diets were restricted to a few foods the composition of which showed little tendency to vary.

The data obtained from subject No. 12 are especially valuable, since he was being underfed and lost 1787 Gm. in the twenty-five days of observation. The calculation was further complicated by a negative nitrogen balance of 1.36 Gm. daily. Nevertheless, the calculated percentage of heat lost by the vaporization of water was 24.7, even though the metabolic mixture was vastly different from the diet.

The response of these subjects, all but 1 of whom remained in bed, was nearly the same as that of the first group, in which the subjects were leading active lives.

The uniformity of performance of these 12 persons indicates that man displays a strong tendency to rid himself, by vaporization of water, of one-fourth of the heat being produced within his body during the twenty-four hours, provided he is comfortable in regard to his environment.

In order to obtain more information about this question, we made use of a large respiration chamber. It was merely necessary to add to its equipment a balance capable of weighing a human being to 1 Gm.

In addition to obtaining the insensible loss of weight, we determined the production of carbon dioxide, the absorption of oxygen, and the urinary excretion of nitrogen. This permitted us to calculate the weight of the water vapor by means of the equation $I.W. = I.L. - (CO_2 - O_2)$ and the heat lost by vaporization of water $(I.W. \times 0.58)$.

The heat production was determined by the standard procedure. The heat production determined by indirect calorimetry was compared with the value derived from the insensible loss of weight.

We performed 39 experiments, each lasting twenty-four hours, on 9 young men and women. Each subject was studied two or more times. One of them was in the third trimester of normal pregnancy. The remainder were presumably healthy persons leading active lives.

The mean values of the twenty-four–hour periods for each of the 9 subjects all fell within the limits of 24.0 and 25.8 per cent.

The calculation of the weight of the water vaporized by persons who are moving about freely is cumbersome, time-consuming, and exposed to errors. However, this difficulty is avoidable since the weight of the water vaporized bears a quantitative relationship to the insensible loss of weight dependent upon the character of the diet. Respiration chamber experiments in which the weight of the CO_2 produced, the O_2 absorbed, and the insensible weight loss were obtained showed that the water vapor is 93 per cent of the insensible loss when the usual mixed maintenance diets are fed. When a high fat diet is taken, the CO_2 and O_2 weigh so nearly the same amount that the weight of the water vaporized accounts for 98 to 100 per cent of the insensible loss of weight. Reduction diets, since they result in a high fat metabolic mixture, have the same effect as high fat diets on the relation between the weights of the water vapor and the insensible loss.

Since the determination of the insensible loss of weight for consecutive twenty-four–hour periods is carried out with ease, and since it has been established that 24.5 per cent of the total heat is dissipated by vaporization of water, a surprisingly simple method is at hand for the calculation of the heat production day after day.

By means of this method we have recorded the heat production of a number of obese persons consecutively for several weeks and sometimes even for months. We have included subjects with various types of obesity described in the literature: (1) a person physically normal except for obesity, who frankly admitted years of gluttony; (2) a feeble-minded girl with a low basal metabolic rate; (3) a girl with disease of the pituitary and a basal metabolic rate 30 per cent below normal; (4) a middle-aged woman whose weight had reached 295 lb. (134 Kg.) after an operation on the hypophysis eight years earlier; (5) a young woman suffering from so-called "Dercum's disease"; (6) a middle-aged woman 5 feet 2 inches (157 cm.) tall whose weight had reached 420 lb. (191 Kg.) (menopausal obesity). In no case did we find anything unusual about the total metabolism. These patients certainly did not exhibit any capacity to live at a lesser expenditure of calories than normal persons. In fact, just the opposite was true. The total expenditure was large and indicated that they produced considerably more heat than persons of the same height, age, and sex whose weight was normal. Our data are entirely in accord with

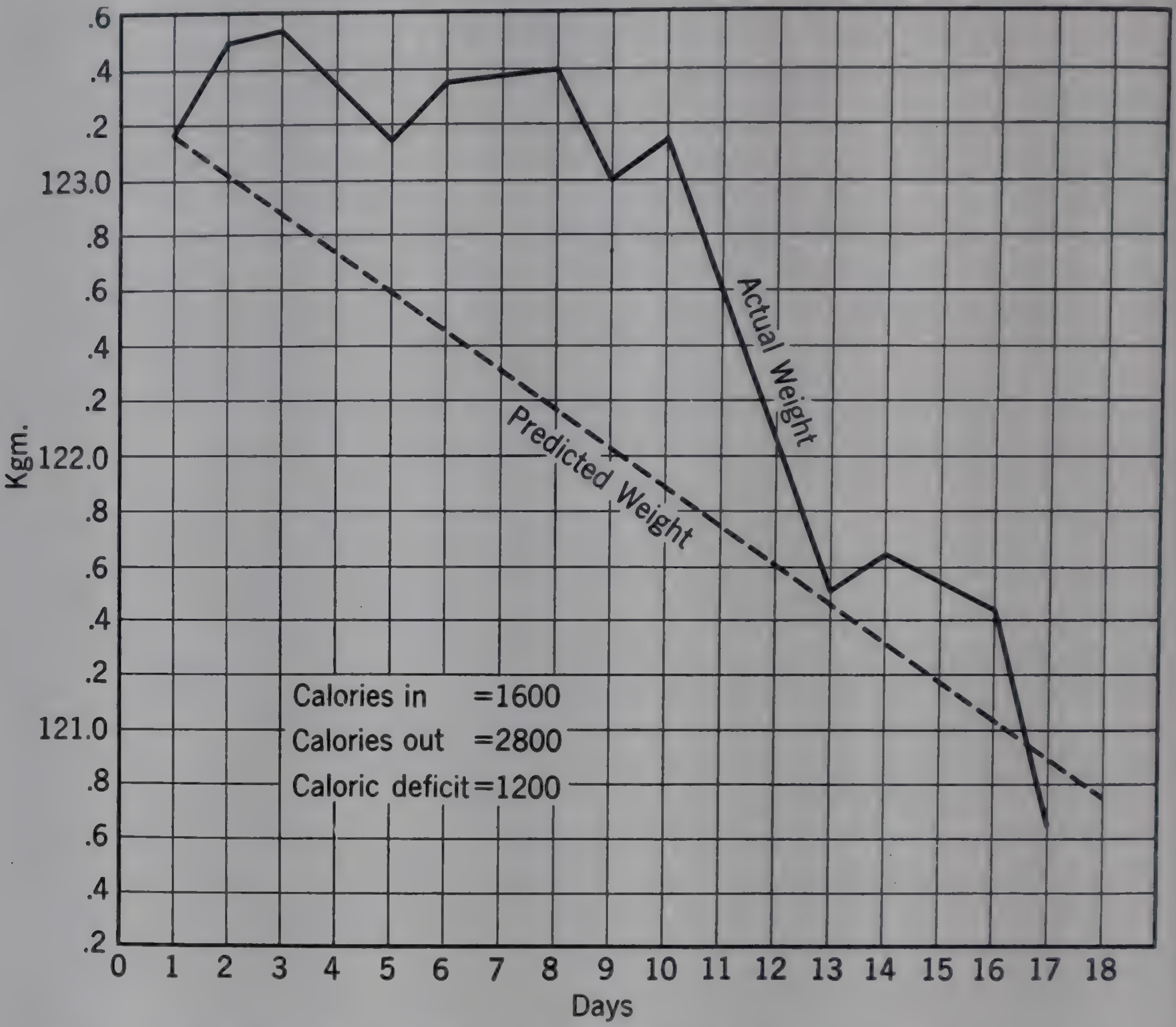

FIG. 29. In spite of underfeeding that caused a destruction of body tissue the weight of which amounted to 150 Gm. daily, the patient weighed approximately as much on the tenth day as she did on the first one. Thereafter, she lost weight much more rapidly than could be explained by destruction of body tissue. This biphasic response to underfeeding suggests that the water content of the organism first becomes abnormally large and then recedes to the normal amount.

those of Lauter,[30] who found that an obese subject requires more energy to perform a given piece of work than does a normal control.

WATER BALANCE

In spite of the large expenditure of energy, we repeatedly encountered periods lasting for a number of days during which the patients failed to lose weight, even though the calories of the diet were far less than the dissipation of heat. A good example of this phenomenon is illustrated by Figure 29.

The patient was a young woman who weighed 275 lb. (125 Kg.) when she entered the hospital. Her basal metabolic rate, which was normal, amounted to 2100 calories per twenty-four hours. Throughout the study she remained in bed. In spite of the inactivity, the total twenty-four–hour heat production averaged 2800 calories.

She received a diet that yielded 1600 calories daily. She was accordingly compelled to oxidize enough body tissue to yield 1200 calories daily. The weight of this tissue was obtained as follows: The patient was placed on the experimental diet one week before the observations began, in order to reduce the carbohydrate stores of the body to the low level after which no more of it would be oxidized to supplement the dietary deficiency. Thereafter, the whole of the caloric deficit was supplied by oxidation of body protein and fat. The amount of body protein destroyed was obtained by subtracting the sum of the urinary and the fecal nitrogen from the nitrogen of the diet and multiplying the difference by 6.25. The number of calories derived from body protein was then subtracted from the total caloric deficit to give the calories yielded by oxidation of body fat, and the value thus obtained was divided by 9 to give grams of fat. Knowing the grams of pure protein and fat oxidized, we needed to convert these materials to the conditions in which they existed in the body in order to arrive at the total weight of the tissues destroyed. Protein in the living organism is associated with three times its weight of water, and fat with one-tenth its weight. When the protein and fat are oxidized, this water is released and excreted. The weight of the tissues destroyed is accordingly the sum of the weights of the hydrated protein and fat. This weight subtracted from the weight of the subject at the beginning of the experiment indicates what he must have weighed on any day if nothing else had intervened to disturb these simple relations. This hypothetic weight is represented in the diagram by the broken line and indicates that about 150 Gm. of body tissue were destroyed daily. The solid line is the actual day-to-day weight of the patient. In spite of the underfeeding, the patient weighed approximately as much on the morning of the tenth day as she did on the first. In fact, she actually gained weight the first and the second day. This capacity to resist loss of weight, even though body tissues are certainly being oxidized and the end products excreted, may last for two weeks or longer. But whatever the duration, it always gives way to a subsequent rapid loss of weight greatly in excess of the weight of the tissue destroyed. In the diagram it will be seen that this patient lost as much weight in three days (tenth, eleventh, and twelfth) as she was expected to lose in twelve days as the result of destruction of body tissue.

It seemed to us, a priori, that this phenomenon might be caused by a retention of water, followed by excretion of the excess. Accordingly, we undertook a study of the water balance.[52]

Table 39 shows the various items that go to make up such a balance.

The moisture content of the food, the urine, and the stools and the weight of water drunk are determined by standard laboratory methods. The weight of the insensible water is calculated from the insensible loss of weight, as previously described. The water of oxidation is that water which arises from the oxidation of the metabolic mixture. The method for calculating the latter from the insensible loss of weight and the excretory nitrogen has already been described. When it is known how much carbohydrate, protein, and fat have been metabolized, the water produced by this process is calculated by multiplying by the factors 0.6, 0.4, and 1.07, respectively. The preformed water is that water which forms an integral part of living tissue. When body tissue is oxidized, its water is released and is added to the mobile water of the body, just as if it had entered through the digestive tract. The method of calculating the number of grams of body protein and fat destroyed has already been described.

TABLE 39. WATER BALANCE

Water available	*Water excreted*
In food	In urine
In drink	In stool
By oxidation	Insensibly
From integral combination with tissues (preformed water)	

In order to control our work we first studied the water relations in a normal subject while he was being underfed. He received 63 Gm. of protein, 26 Gm. of fat, and 148 Gm. of carbohydrate, yielding 1078 calories. He produced 1688 calories daily, derived from 69 Gm. of protein, 91 Gm. of fat, and 148 Gm. of carbohydrate (averages for each twenty-four hours). Consequently, he destroyed 6 Gm. of body protein and 65 Gm. of body fat each twenty-four hours. The combined weight of these two substances in their hydrated living state is 95 Gm.

It was soon noticed that this man, even though normal, failed to lose weight smoothly. Like obese persons, for several consecutive days he would lose no weight or he might even gain weight. Then his weight would suddenly decline at a rapid rate far in excess of 95 Gm. daily.

Table 40 shows the water exchange for five consecutive days when the subject weighed 115 Gm. more at the end than he did at the beginning, even though he had destroyed 450 Gm. of body tissue. It is quite clear that the failure of the body weight to keep pace with the loss of tissue is attributable to the retention of water.

Since these events took place in a normal subject, they are deprived of all specificity for obese subjects. The excessive retention of water is seen to be merely a by-product of undernutrition. It in no way indicates that the metabolism of obese persons is abnormal.

Table 40. CONCEALMENT OF DESTRUCTION OF TISSUE BY RETENTION OF WATER

Day of experiment	*Change in weight of subject* Gm.	*Weight of body tissue destroyed* Gm.	*Water balance* Gm.
1	+285	90	+369
2	−225	90	−105
3	+ 65	90	+149
4	−125	90	− 41
5	+115	90	+198
Totals	+115	450	+570

In order to leave no doubt that the failure of obese persons to lose weight is explained by retention of water, the following case is cited:

The patient was a girl aged 14 who had always been taller and fatter than the girls of her age. Her progress in school had been slow, and she had repeated many of her grades. She freely admitted overeating and said that she much preferred sitting quietly without occupation. Menstruation had begun when she was 10 years old and had been regular. She was 6 feet 1 inch (185 cm.) tall and weighed 244 lb. (111 Kg.). There was a luxuriant growth of axillary and pubic hair, and the breasts were large. Her tongue was exceptionally thick and broad. This girl was selected for study because she was obviously an abnormal type. Nevertheless, it will be seen that her failure to lose weight was attributable to retention of water. The diet consisted of 65 Gm. of protein, 40 Gm. of fat, and 74 Gm. of carbohydrate. It contained 914 calories. She produced 2137 calories daily by metabolizing 73 Gm. of protein, 172 Gm. of fat, and 74 Gm. of carbohydrate. Therefore, the daily destruction of body tissue amounted to 181 Gm. Figure 30 shows her response to the underfeeding for 20 consecutive days. It will be noted that she weighed as much on the sixteenth day as she did at the start. Then a marked diuresis set in without any other change in the conditions. The diuresis continued for the next nine days of the study, by which time she had lost an amount of weight approximately equal to the weight of the body tissue destroyed during the twenty-four days. The solid line in Figure 30 indicates the actual weight each morning. The broken line states what she would have weighed in response to the destruction of body tissue if the water balance had not been disturbed. The position of the circles was calculated by subtracting the weight of the extra water in her body from the actual weight. They show that her ability to resist loss of weight for more than two weeks was caused by progressive addition of water.

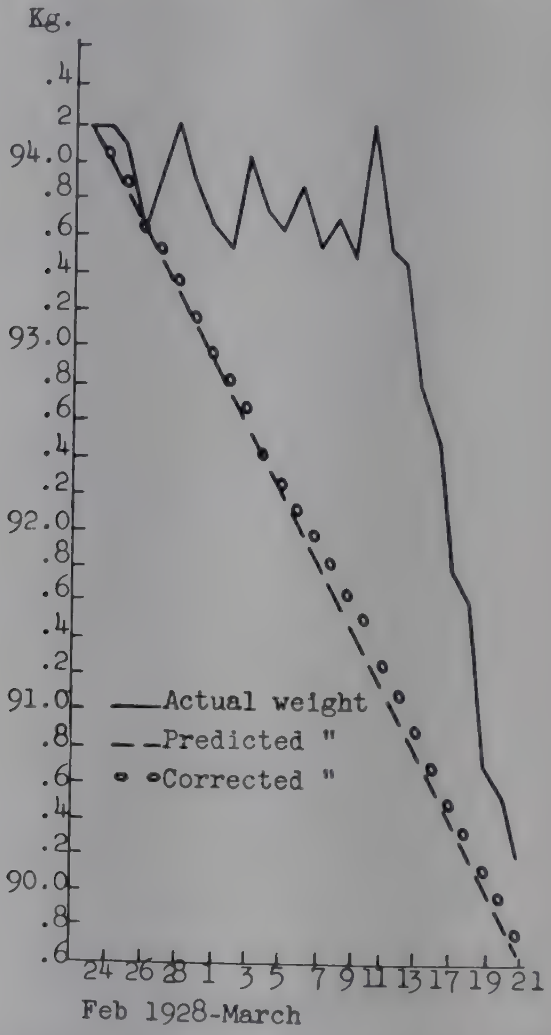

FIG. 30. A response similar to that portrayed in Figure 29. The circles represent the body weight corrected for water retention. The retention of 2,900 grams of water in sixteen days explains the failure to lose weight.

INCREASED ABSORPTION OF FOOD

After it had been generally accepted that obese persons produce more heat than normal controls, the possibility still remained that if the digestion and absorption of food by the obese persons were sufficiently more efficient than that by normal people, the former could succeed in gaining weight without overeating. Neuenschwander-Lemmer[31] has investigated this possibility. He compared the combustible materials in the feces with those in the diet. In a patient 5 feet 4 inches (163 cm.) tall who weighed 231 lb. (105 Kg.) he found 4.96 per cent of the nitrogen and 14.9 per cent of the fat of the diet in the stool. A control of the same height who weighed 125 lb. (57 Kg.) lost 5.49 per cent of the dietary nitrogen and 11.7 per cent of the fat in the stool. The residual calories in the feces of a group of obese persons were 5.47 per twenty-four hours, as compared with 5.41 in persons of normal weight. The utilization of the dietary calories, nitrogen, and fat by the obese persons was 87, 84, and 83 per cent respectively. For the controls, the corresponding values were 88, 86, and 89 per cent. Obesity is not caused by an economy of food.

"LIPOPHILIA"

Von Bergmann suggested that adiposity is caused by a hereditary constitutional trait of the adipose cells that enables them to accumulate excessive amounts of fat. Hetenyi[26] carried this idea one step further by postulating that fat once deposited in the depots of an obese person is prevented from leaving them and so cannot be used as fuel. Increased appetite is the natural response.

If it were true that the adipose tissue cells of obese persons resist mobilization of fat in undernutrition, then such persons would not lose weight, or, if they did, the loss would represent the destruction of body protein. But the following studies show that obese persons are less likely to go into negative nitrogen balance when underfed than are normal subjects. Jansen[27] placed 15 medical students whose average weight was 62 Kg. on a diet yielding 1600 calories and 61 Gm. of protein daily for several weeks. Their average loss of nitrogen was 2 Gm. daily. Benedict's[3] 12 normal subjects receiving 1534 calories and 51 Gm. of protein lost 65 Gm. of nitrogen from the body in three weeks. On the other hand, Strang, McClugage, and Evans[48] found that obese persons receiving only 440 calories and about 1 Gm. of protein per kilogram of ideal body weight do not lose body protein.

With these things in mind, Malcolm Block has reinvestigated the response to underfeeding. He estimated the caloric deficit by comparing the energy of the diet with the expenditure of energy. The differences were then converted to weight of body tissue destroyed, on the assumption that it consisted entirely of fat. The results for the 3 obese patients are found in Table 41, which also records the daily intake of nitrogen and the urinary nitrogen. It will be seen that each of the patients lost almost exactly the amount of weight that she would be expected to lose if the body tissue destroyed to make up the caloric deficit were solely adipose tissue. Furthermore, the comparison between the dietary and the urinary nitrogen shows the patients lost only negligible amounts of body protein.

TABLE 41. LOSS OF WEIGHT AND DAILY DIETARY INTAKE AND URINARY OUTPUT OF NITROGEN IN THREE OBESE SUBJECTS

	Daily loss of weight Gm.		*Daily nitrogen*	
No. of Subject	Predicted	Actual	*Intake in diet* Gm.	*Output in urine* Gm.
13	254.6	255.4	13.81	14.34
14	250.7	249.2	13.81	13.35
15	222.8	222.8	13.66	13.75

These later studies show that obese persons release fat from the stores as a source of energy as readily as normal persons do. In fact, it seems likely that the obese persons do this more readily, since they usually remain in nitrogen balance when they are underfed, whereas persons of normal weight do not.

The fasting respiratory quotients in obese persons are lower than those in normal controls. According to the usual interpretation, this means that the former persons are oxidizing more fat. Quotients published by Strang[45] are enlightening. The fasting values obtained from 7 obese patients ranged from 0.698 to 0.830 and averaged 0.757. The controls under similar conditions ranged from 0.770 to 0.848 and averaged 0.783. These same persons were studied again after a test meal consisting of 40 Gm. of protein, 26 Gm. of fat, and 52 Gm. of carbohydrate. Quotients were obtained repeatedly for eight hours after the meal and are presented in Table 42.

TABLE 42. RESPIRATORY QUOTIENTS AFTER A TEST MEAL

			Hours after meal			
	1	2	3	4	6	8
Normal subjects	838	810	804	823	812	819
Obese subjects	746	772	752	740	761	795

Since both the quotients obtained during fasting and those obtained after the ingestion of food are lower in obese subjects, we have before us classic evidence that such persons are metabolizing more fat than the normal controls. They cannot at the same time be storing more fat or withholding more of it in the depots.

SUMMARY

These many painstaking investigations of the metabolism of obese persons have failed to disclose any abnormal process that accounts for the accumulation of fat. On the contrary, they have demonstrated that obese persons produce more heat in the basal state, that they expend more energy to perform a measured amount of work, and that their total heat production is greater than that of normal persons of similar age, height, and sex under the same circumstances. Since they are unable to absorb more energy from their food, they must eat more than normal people simply to avoid loss of weight.

ENDOCRINE DISORDERS AND OBESITY

In an age when the vast influence of the internal secretions on bodily states is being emphasized by a host of workers, it is but natural that various endocrine glands have been accused of causing obesity.

THYROID

Those writers who believe that the endocrine etiologic basis of obesity has been established have expressed opinions that hypothyroidism is a frequent cause of adiposity. They based the diagnosis on a basal metabolic rate of −10 to 25 per cent, with or without feelings of sluggishness, coldness, and ease of fatigue. But these subjective complaints are so vague and commonplace that they are of almost negligible diagnostic import.

Before interpreting a low basal metabolic rate as a pathognomonic sign of hypothyroidism it is essential to recall some of the details of the test. In the first place, the apparatus records solely the amount of oxygen absorbed in a unit of time by the patient. To compare this value with a standard, the surface area of the patient must be calculated from his height and weight in order to obtain his absorption of oxygen per square meter of his body surface. This value is then compared with the average absorption per square meter of presumably normal persons of the same sex and age. These control subjects are assumed to have been completely relaxed during the test. But if some of them were not because they were a little apprehensive or uncomfortable, then the standards in general use are too high. Those best qualified to judge do, in fact, state that the standards are 5 per cent or even 10 per cent too high. Hence, a patient whose basal metabolic rate is reported as −10 per cent may be merely one who is completely relaxed or who has fallen asleep. (Sleep lowers the rate 10 to 15 per cent.) Most of the investigators in this field have rates 10 per cent or more below the alleged normal for them, and they are probably merely demonstrating that their familiarity with the technic permits a degree of relaxation that was assumed to have occurred, but may not have, in the controls.

Some persons who are entirely at home in the metabolic laboratory have rates year after year that are 20 or even 25 per cent too low according to the standards, and still they exhibit the attributes of health and have not become obese or myxedematous.

The custom of paraphrasing a low metabolic rate by the term "hypothyroidism" is not justifiable and certainly is misleading. If a physician wants to give a clinical interpretation to the phenomenon of lessened rate of absorption of oxygen, he can speak of hypometabolism without saying more than the facts justify. He will then be in the same position as when he deals with fever or leukocytosis. He will know that these abnormalities mean little by themselves but that when they are associated with certain other signs of disease, and only then, is he justified in making a diagnosis.

Finally, it must be emphasized that even low basal metabolic rates need not cause obesity. The organism, at least in the ideal state, obtains the amount of food that will replenish its losses. When the outgo lessens, appetite diminishes proportionately. This relation between expenditure and intake is shown beautifully by some recent experiments carried out by MacKay and Sherrill.[33] They introduced their data on rats with the remark: "Although it is well known that patients with myxedema are not obese as a rule, the idea persists in the clinical literature that hypothyroidism may be a cause of obesity."

In order to observe the effect of complete absence of the thyroid hormone, the gland was removed from a group of rats 170 days old. A similar group was selected for control, and all the animals were offered the same diet ad libitum. Three hundred and ten days later the controls weighed 457 Gm. and had gained 193 Gm. But the thyroidectomized animals gained only 178 Gm. Still more interesting was the difference in the fat content of the two groups. The bodies of the controls contained 31.1 per cent of fat, whereas only 6.4 per cent of fat remained in the bodies of the rats deprived of their thyroid glands.

Even more enlightening is the recent statistical investigation of this general question by Plummer[40] on 200 patients suffering from various grades of myxedema. Of these 61.5 per cent were overweight. In 8.5 per cent the weight was more than 50 lb. (23 Kg.) above normal, but in 5.5 per cent it was more than 30 lb. (14 Kg.) below normal. The greatest excess weight corresponded to the least depression of metabolism, and those patients whose basal metabolic rates were lowest weighed the least. Thus those whose rates were not less than −28 per cent weighed 11.5 per cent too much, whereas those whose rates were less than −38 per cent weighed 14.7 per cent too little. The average excess weight for the whole group was 10.1 lb. (4.5 Kg.). During the first days of medication with thyroid there was an abrupt loss of weight averaging 13 lb. (6 Kg.). This was brought about by elimination of fluid, since most of the patients were definitely edematous prior to treatment. Now the group weight had become 2.9 lb. (1.3 Kg.) less than normal. The excessive weight so commonly attributed to superabundance of adipose tissue is more properly interpreted as evidence of abnormal accumulation of water. In fact, judging by MacKay's rats, athyrea causes wasting of adipose tissue.

Pituitary

Fröhlich's[20] report in 1901 of a case of tumor of the hypophysis without acromegaly seems to have given rise to the belief that hypopituitarism is a common cause of obesity, especially among children. He described a boy 14 years old, weighing 54 Kg., who for two years had been suffering from attacks of vomiting and headache. The left eye had become blind. The mother stated that the boy's weight had begun to increase rapidly a few months earlier. The examination revealed atrophy of the left optic nerve and right temporal hemianopsia, evenly distributed adiposity, enlargement of breasts, absence of axillary hair, pubic region suggestive of feminine type, and dryness and local thickenings of skin. Fröhlich concluded that the rapidly developing obesity should be accepted as a sign of hypophysial tumor. The author cited a number of cases of similar condition proved at autopsy, but he also pointed out that poor nutrition was not uncommon in other cases of proved hypophysial tumor. Certainly there is nothing in this original report to indicate that the obesity was anything more than incidental, especially since the author himself stated that emaciation is commonly encountered in cases of hypophysial tumor.

Cushing attributed the syndrome that goes by his name to adenoma of the basophilic cells in the anterior hypophysis. Patients with this syndrome often exhibit a disproportion between the trunk and the extremities because of the increased girth of the chest and abdomen. Cushing attributed the enlargement of the trunk to excessive deposits of fat and reasoned that a localized adiposity could not arise from overeating but must be a direct outcome of the disease of the pituitary.

Cushing is but one of many writers who have suggested or even asserted that the obesity associated with dyspituitarism results from some

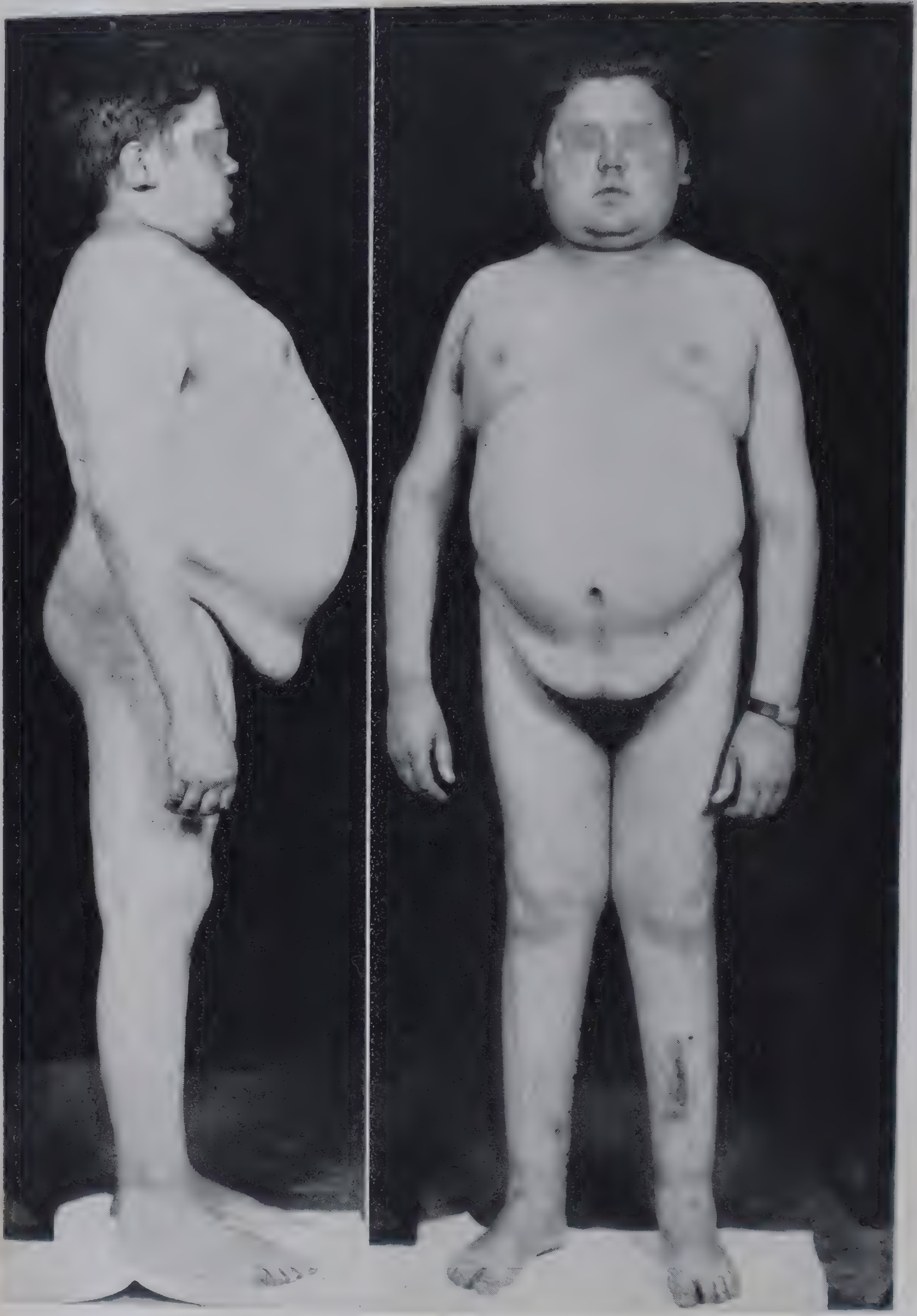

Fig. 31A Fig. 31B

FIG. 31. A patient with Cushing's syndrome. *A* and *B*, note the appearance of extreme obesity with an excess weight of only 50 pounds (23 Kg.).

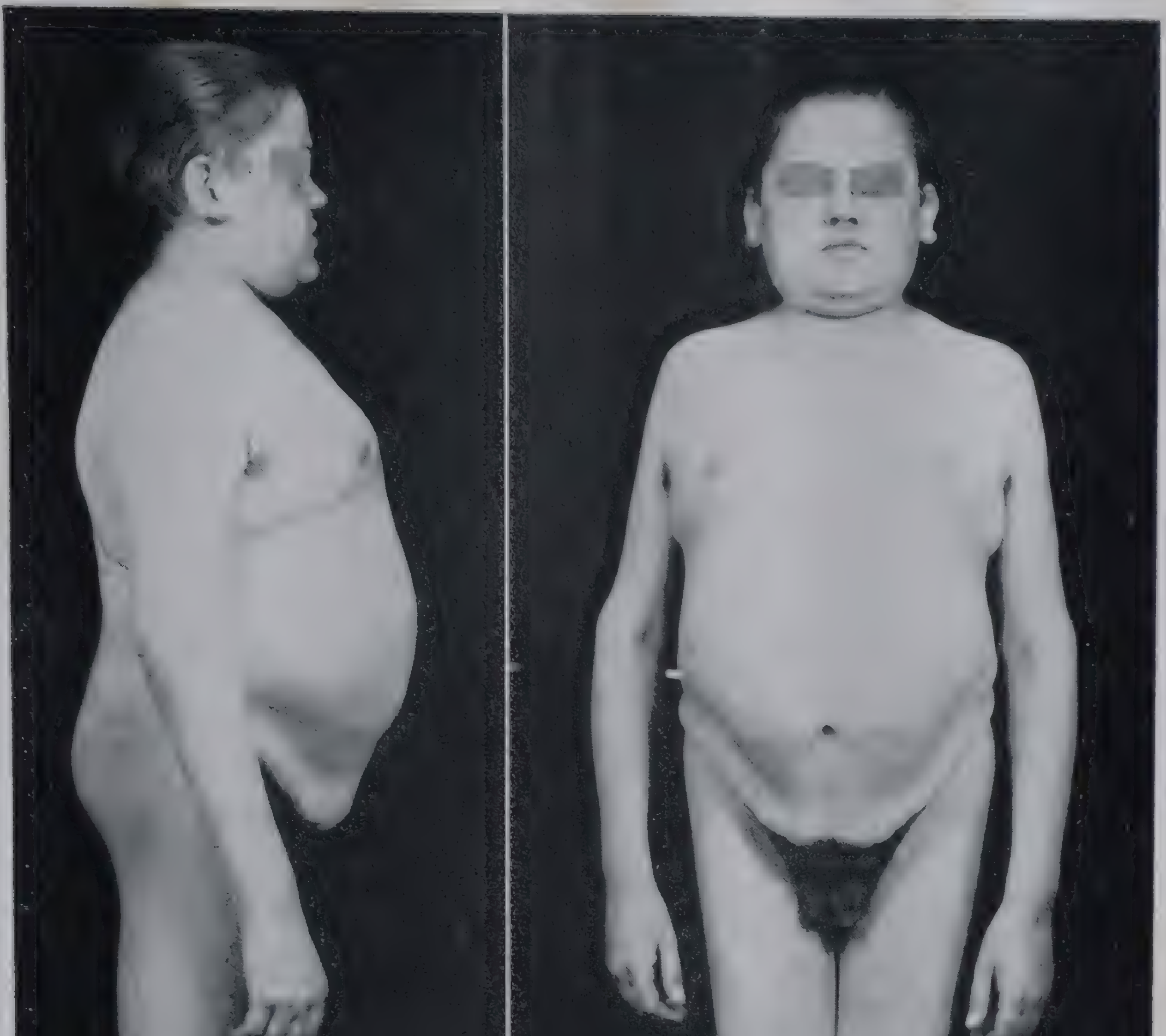

Fig. 31C Fig. 31D

Fig. 31 (*continued*). *C* and *D*, the same patient after reduction of the weight to normal. Nevertheless, the semblance of obesity persists.

unusual metabolic disturbance which in a mysterious way causes an increased synthesis and deposition of fat.

Three associates and I[19] have recently had the opportunity of studying a case of Cushing's syndrome in which subsequent postmorten examination disclosed a basophilic adenoma of the pituitary, but we arrived at a different explanation of the abnormal bodily shape. The data that deal with the patient's configuration are reproduced here because they show that the protuberance of the thorax and the abdomen was caused by a condition totally unrelated to adiposity.

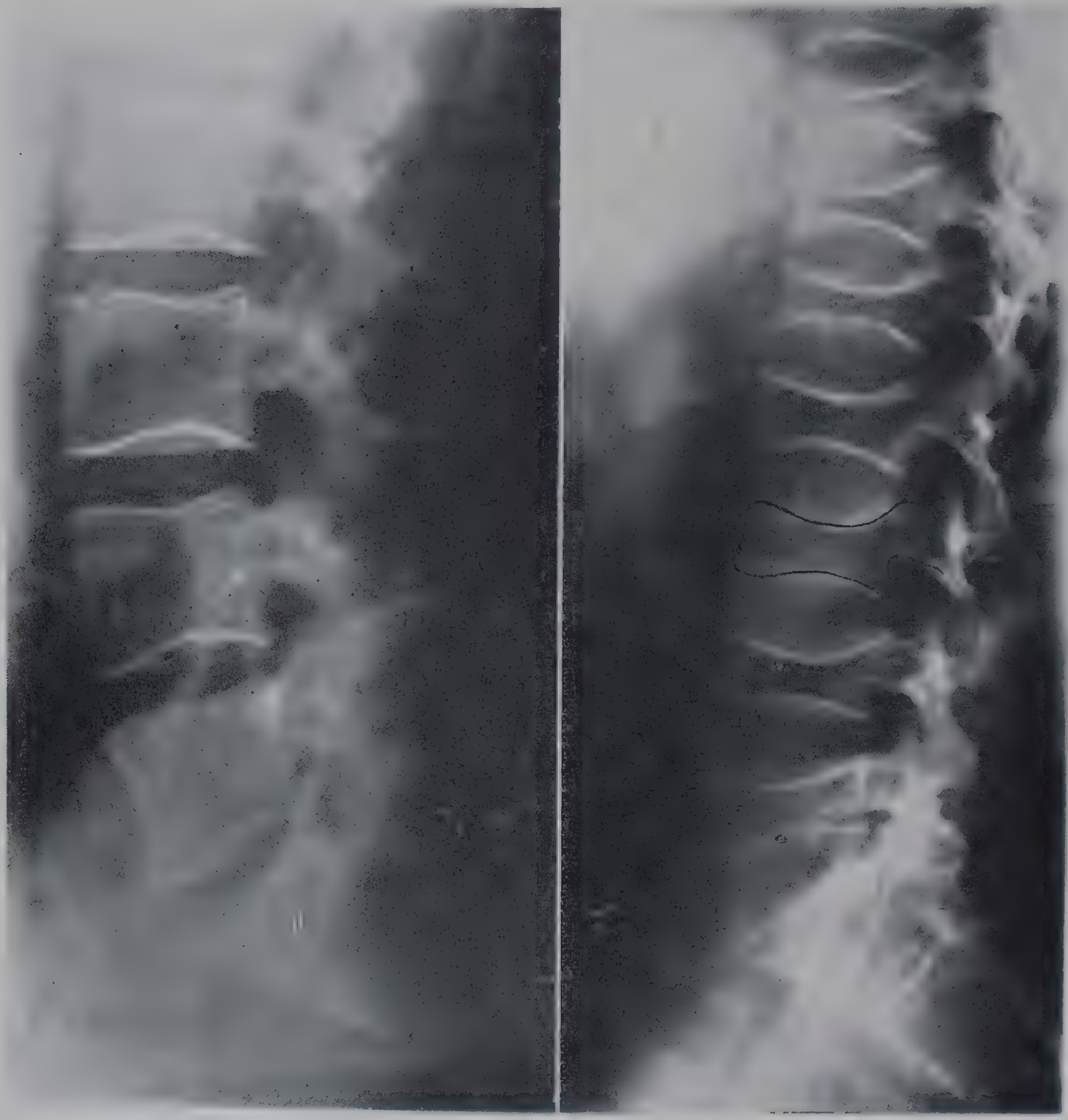

Fig. 32A Fig. 32B

FIG. 32. Lateral roentgenograms of spinal columns. *A*, normal control. *B*, the patient in Figure 31. Note how decalcification has caused thinning of vetebral bodies and shortening of the spine (fish vertebrae).

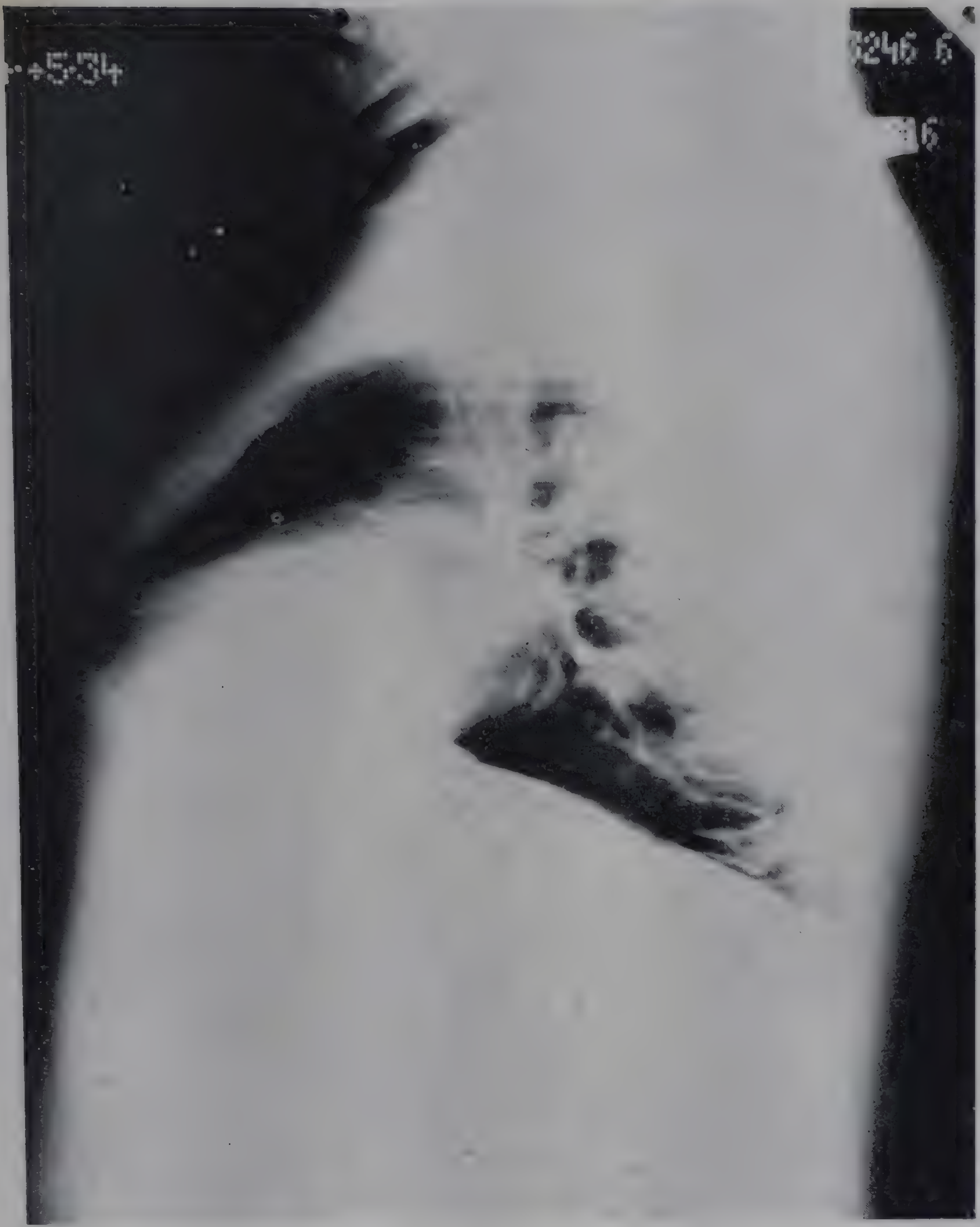

FIG. 33. Lateral roentgenogram of the thorax of the patient in Figures 31 and 32*B*. The ribs are horizontal because of shortening of spine. This has forced the lower end of the sternum upward and forward, carrying the anterior half of the diaphragm with it. The marked increase in the anteroposterior dimension of the thorax is evidenced by the horizontal position of the heart.

As a child, the patient enjoyed exceptionally good health. When he was 12 years old he began to gain weight rapidly. At the age of 19, when he entered the hospital, he weighed 185 lb. (84 Kg.) and was 5 feet 2 inches (157 cm.) tall. His appearance at that time is portrayed in Figure 31.

As part of the study he was placed on a diet the composition of which was the same for fifty-four days. It supplied 890 calories daily. The heat production was calculated from the insensible loss of weight and the urinary nitrogen. From these data we predicted that he should have lost 8376 Gm. He did lose 8398 Gm. This remarkably good agreement indicated that the energy exchange was entirely normal.

The loss of 50 lb. (23 Kg.) and the return to normal weight altered little the appearance of the unusually prominent chest and abdomen and did not reduce their size any more than that of the extremities. Hence, the disproportionate enlargement of the trunk could not have been due to obesity. A lateral roentgenogram did, however, reveal the actual reason for the deformity (Figs. 32 and 33). The decalcification of the skeleton, a common finding in Cushing's syndrome, had so thinned the vertebrae that the spine had collapsed, with resulting kyphosis and shortening to the extent that the ribs had been elevated anteriorly until they were horizontal. This had swung the manubrium forward and upward. The anterior abdominal wall necessarily also moved forward. A perfect explanation for the enlargement of the trunk had been found without involving obesity. In fact, scrutiny of the cases brought together by Cushing and more recently by Freyberg reveals that obesity was not prevalent. Rather were the patients disfigured by protruding abdomens, barrel chests, short necks, kyphosis, and wasted musculature.

It is of further interest that the penis and scrotum of our patient were almost invisible on admission. This appearance is held to be characteristic of Fröhlich's disease (adiposogenital dystrophy). However, when the weight had been reduced, the penis and testes had assumed the usual appearance.

Two recent publications present further evidence that the abnormal bodily configuration in patients suffering from Cushing's syndrome is not dependent on adiposity. Willson, Power, and Kepler[54] discussed a patient who had lost 25 lb. (11 Kg.) during the four weeks before he entered the clinic, at which time he weighed 118 lb. (54 Kg.). The accompanying photograph (Fig. 34) leaves no doubt about the emaciated state of the patient. Nevertheless, the abdomen bulges to a striking degree, and the authors spoke of the characteristic plethoric moon face. The origin of these abnormalities is explained satisfactorily by Albright without attributing them to increases in adipose tissue, as will appear shortly. Albright, Parson, and Bloomberg[1] studied 3 women with Cushing's syndrome and emphasized the apparent girdle obesity, "which is more the result of a relaxed abdominal wall and crushed vertebrae (decalcification) than of actual fat." Two of the women weighed 118 lb. (54 Kg.) each. Certainly they were not obese. Nevertheless, the photograph of one of them does give the appearance of the so-called "girdle obesity" (Fig. 35). Albright and associates pointed out that there is a striking destruction of body protein in these patients, as evidenced by the continued negative nitrogen balance. Under such circumstances, a great

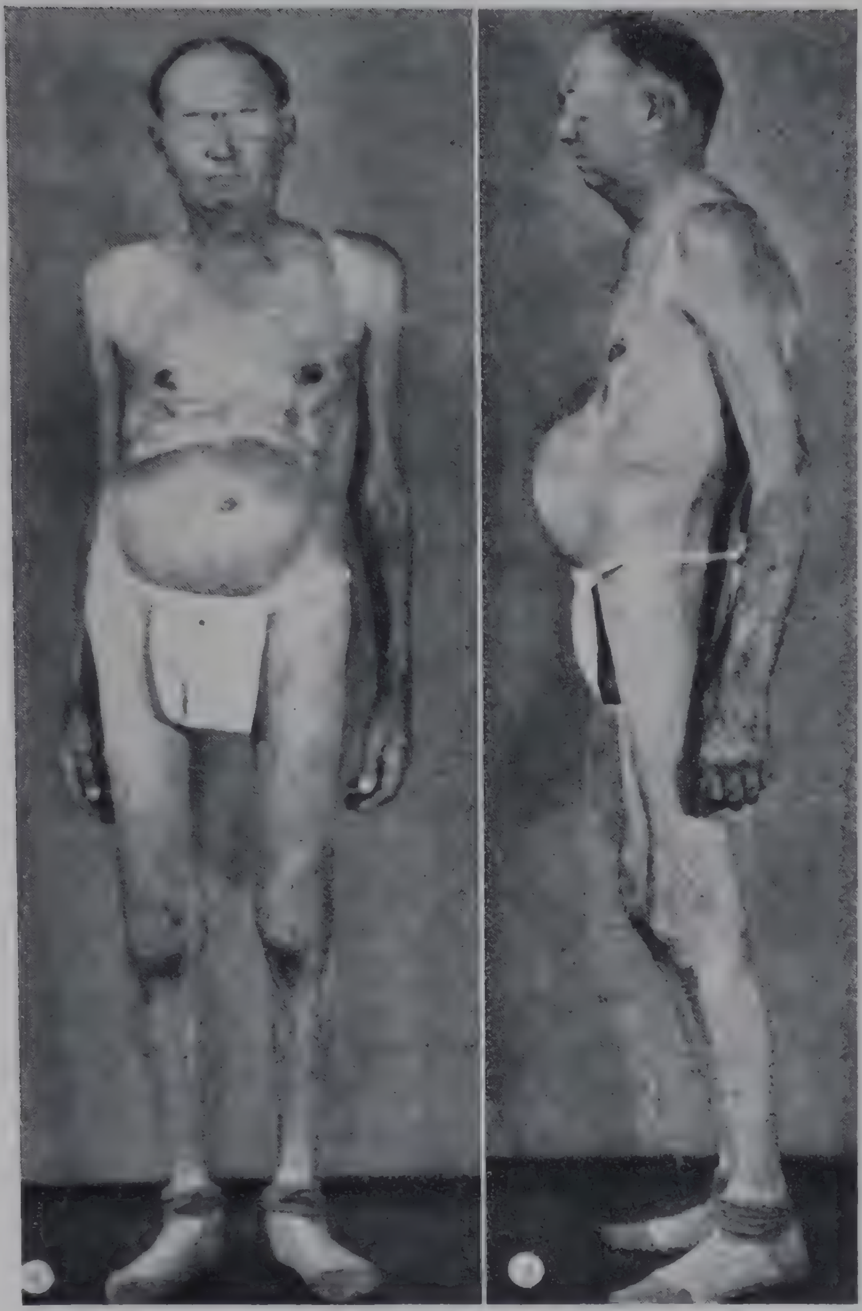

FIG. 34. Note the bulging abdomen in spite of emaciation. The spinal deformity in this patient caused pronounced lordosis. (From Willson, D. M., Power, M. H., and Kepler, E. J.[55])

wastage of the musculature takes place and the abdominal muscles are no longer able to resist the intraabdominal pressure.

During the early years of this century, other investigators in addition to Cushing endeavored to elucidate the functions of the pituitary by observing the effects of its removal. Opinion was divided. Like Cushing, several other investigators expressed the belief that they had demonstrated that hypophysectomy caused obesity. But Bailey and Bremer, as well as Camus and Roussy, were in doubt, since they found that injury of the

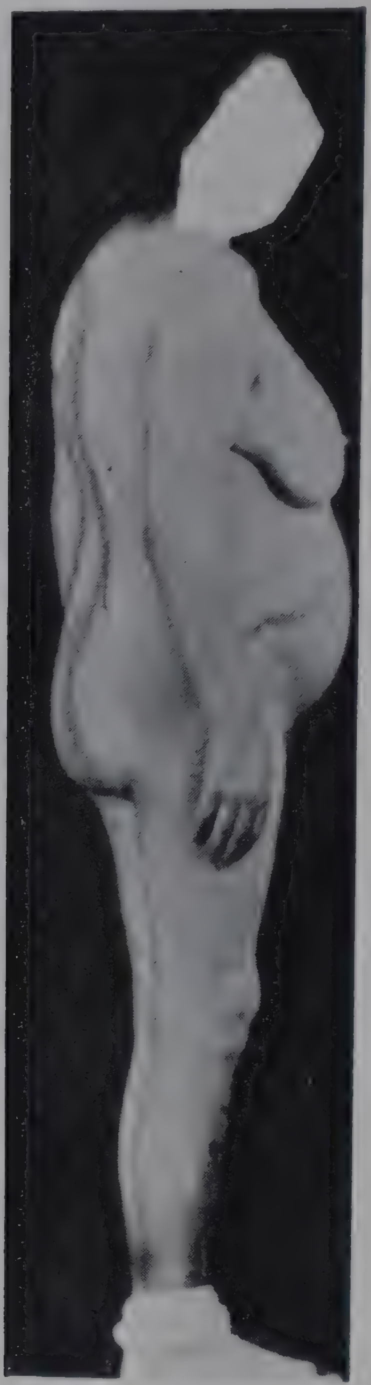

FIG. 35. Apparent girdle obesity caused by muscular atrophy. (From Albright, F., Parson, W., and Bloomberg, E.[1])

brain adjacent to the pituitary was also capable of producing excessive depositions of fat. Finally, it was conclusively demonstrated by Philip Smith,[43] working with rats, that the removal of the hypophysis from these animals did not cause obesity. However, when the hypothalamus was injured by injection of chromic acid, obesity developed regularly after the operation. Smith explained the occurrence of obesity in the dog and its absence in the rat by pointing out that the hypophysis in the dog is separated from the brain by only a gauzelike membrane which invariably ruptures during the operation, whereas in the rat the membrane is firm and resistant. In his operations on the rat, the membrane remained intact and hypophysectomy invariably produced loss of weight, atrophy of the thyroid, the adrenal cortex, and the sex organs, and cachexia.

Knowledge is now sufficiently advanced to permit the recognition of hypopituitarism when sufficient skill and effort are devoted to the clinical study. The disturbances sought for are based on the recognition that the anterior lobe of the pituitary secretes hormones which control the activity of the thyroid, the adrenal cortex, and the gonads, as well as the utilization of dextrose. Its ablation in young animals causes cessation of growth in addition to atrophy of the glands just mentioned. In the adult human being the disease described by Simmonds and shown by him to be due to destruction of the anterior lobe of the pituitary presents the counterpart of the condition produced by experimental ablation of the hypophysis. Here also, the most prominent features are emaciation and atrophy of the thyroid, the adrenal cortex, and the gonads. Even diminished function is also recognizable, since it produces clinical pictures that suggest myxedema, Addison's disease, various signs of lessened activity of the reproductive glands, and hypoglycemic episodes, present in various combinations from patient to patient. Obesity is not a feature of any of these states.

HYPOTHALAMUS

Ranson and his associates[41] placed lesions in the hypothalamus in nearly 50 monkeys, 300 cats, and many guinea pigs without obtaining obesity. Subsequently, they injected chromic acid into the hypophysis in rats by a technic that they hoped would avoid the hypothalamus. Only 3 of 50 rats became fat. Hypothalamic lesions of considerable extent were found in these 3 animals. The hypophysis showed all degrees of destruction in the 47 rats in which obesity did not develop. In another series they used the Horsley-Clarke instrument, which permits accurate localization, to place lesions in the hypothalamus in 12 rats. All became markedly obese. Subsequent examination revealed large lesions in the hypothalamic area. The hypophysis was intact. These experiments have excluded lesions of the pituitary as a cause of obesity in lower animals, and they cast formidable doubt on the proposition that obesity in human beings is ever originated by destructive disease of the hypophysis.

The animal experiments seem to have demonstrated that lesions of the brain in the hypothalamic area are regularly followed by development of obesity in rats. But perhaps of more importance is the failure to produce obesity in the other mammalian species in which the hypothalamus was injured. The negative results obtained by Ranson and associates on a large number of monkeys cast a good deal of doubt on the proposition that hypothalamic lesions in human beings are the actual cause of the obesity sometimes seen in patients afflicted with disease of that portion of the brain.

JUVENILE OBESITY

Many obese children are assumed to be suffering from hypopituitarism (Fröhlich's syndrome) or hypothyroidism, even though one searches in vain for sufficient facts to support the contention. Bruch's[10] dispassionate study of these questions is therefore welcome. Her material consisted of 102 patients, equally divided among girls and boys, 2 to 13 years old, in whom obesity was the outstanding clinical condition. Weight at birth was normal; normal development was the rule, and puberty was attained at normal age or earlier. Obese children are taller than normal ones, and skeletal growth, as determined by roentgen rays, is accelerated. Normal girls who menstruate early are taller and heavier than those in whom the onset is later. Bruch concluded:

> The condition of the obese children manifests an exaggeration of a developmental trend observed in normal children; the difference is only quantitative . . . the growth and development of obese children . . . cannot be brought into agreement with the well defined picture of hypothyroidism [or] . . . hypopituitarism. . . . It is not reasonable to explain accelerated development as resulting from hypofunction of glands the growth-promoting qualities of which are firmly established. . . .

Nevertheless, the treatment of choice, and often the only therapy of the children referred to the obesity clinic, was administration of endocrine products, according to Bruch. When a physician had recommended pituitary preparations, he had done so because he had made a diagnosis of adiposogenital dystrophy, basing it on the presence of adiposity coupled with retarded development of the genitalia. But recent studies have made it clear that genital infantilism is far less common than is widely believed. In this connection, Bigler, Hardy, and Scott[6] pointed out that the incidence of undescended testicle in the United States Army is 0.3 per cent, whereas at the Hospital for Ruptured and Crippled, New York, incomplete descent was diagnosed in 3.0 per cent of 18,000 children. This means that in 9 of every 10 children in whom the diagnosis is made, the testicles will subsequently descend spontaneously. Browne[9] called attention to a series of misconceptions which lead to incorrect diagnosis. He states that any position from which the testes will reach the scrotum is normal and that the belief that a testicle which can be felt in the region of the inguinal canal is in that canal is a common mistake. Gonadotropic substances will not bring down a testis that would not have descended without such treatment. Its only power is to hasten descent. Spencer and Scowen[44] confirmed Browne's findings. Accordingly, the descent of a testicle in a fat boy after treatment with gonadotropic substances should not be accepted as evidence that he was suffering from hypopituitarism. Bruch stated that in none of her patients who had been made miserable and unhappy by a diagnosis of sexual maldevelopment was this diagnosis justified.

HEREDITY

The interesting observations published by Danforth[12] proved that in at least one mammalian species there exists a gene that, with great regularity, causes its possessor to become obese. Yellow male mice were mated to females of various colors. Some of the descendants were yellow, others were not. Litter mates were kept in the same cage and had access to the same food. After sexual maturity had been attained, the yellow mice began to gain weight more rapidly. This was especially true for the yellow females, many of which reached a weight twice that of their mates. The excess weight was mainly due to a great and widely distributed increase in adipose tissue. Our own studies, still in a preliminary state, of this hereditary obesity of yellow mice permit the statement that the mice which become obese eat more than the others. Evidently one is dealing with a hereditary bulimia.

Before considering whether a similar gene is transmitted by human beings, it will be well to give some thought to the configuration of the body. No one questions the inheritance of bodily shape or build. Everyone is familiar with the characteristic lines of purebred dogs. One has merely to recall the contrasts between the slender, graceful, agile greyhound and the thick-set, ponderous English bulldog. But even though the bulldog is robust and powerful, he is not obese. He may, however, be pampered into overeating and become so.

Similarly, the human being who has inherited asthenic build is not predestined to become obese. Pains must be taken to explain to him that the two qualities are not linked—that while shape is inherited, obesity is an acquired characteristic.

Adipose tissue is much more abundant in some parts of the body than in others, and women normally possess more fat than men. Furthermore, there is commonly a large accumulation of fat around the hips and loins of women of normal weight. And since the pelvis of a woman is flatter than that of a man, she starts with two handicaps when she becomes obese. The so-called "girdle" obesity merely accentuates a normal type of feminine configuration. While it may well be true that the deposition of the excessive fat in the central regions of some women is an inherited characteristic, it is also true that there would have been no extra fat to deposit in those regions had the intake of food not been overabundant.

The prevalence of obesity in some families need not be accepted as an inherited and therefore an unavoidable trait. A more realistic explanation is the continuation of the familial tradition of the groaning board and the savory dish.

The question of whether human obesity is an inherited characteristic has been investigated extensively. Such studies are based on the proposition that identical twins are genetically identical throughout and that differences in the individuals of such a pair are due to environmental influences. Accordingly, differences in body weight are caused by environmental influences. Both Verschuer[50] and Newman and associates[36] found that weight varied more than any of the other anthropologic measurements. In fact, the average variation in weight was always at least twice, and usually three times, as great as that of any of the other variables. This emphasizes the important influence of environment on weight.

Furthermore, Verschuer compared the variations among identical twins living under similar conditions with those among twins living under dissimilar conditions. Differences in weight were two and a half times as great when environment was dissimilar.

SUMMARY

It is hoped that the foregoing discussion has convinced the reader that obesity is never directly produced by increased or diminished activity of an endocrine gland. In other words, no internal secretion is capable of so changing the metabolism that the total amount of fat in the body will increase unless the inflow of calories is greater than the outflow.

It remains for the future to decide whether a hypothalamic disorder or other cerebral disease is capable of causing human obesity through abnormal stimulation of appetite. Whatever the answer, the simple principle will remain that obesity is invariably the result of a disproportion between the inflow and the outflow of energy. The former must always be greater than the latter, either because the intake has increased or the outgo has diminished.

Body build is inherited; obesity is not.

HUNGER AND APPETITE

In the ideal state the living organism is directed by hunger to secure food in amounts sufficient to replenish the bodily materials that have been destroyed by oxidation or have been excreted. This primitive mechanism does not give rise to sensations which are primarily pleasurable. It is, so to speak, more businesslike than that. With the passage of time hunger has come to be so closely associated with other feelings called appetite that the mind of man no longer distinguishes clearly between the two. Appetite, strictly speaking, is a sensation produced by happy memories. The desire for food may be the expression of real hunger, but it is more generally a response to habit or the anticipation of pleasure.* It is modulated by the emotions to a striking degree. Fright, fear, sorrow, illness, and displeasing sights and smells depress or even abolish it. It is stimulated by foods that give off pleasant odors, that please the eye and the palate. Happy recollections and good companionship are conducive to overeating. It may be that the long-established habit of eating certain quantities of food has a more profound influence on the appetite than does the intervention of lessened physiologic needs associated with hypofunction of an endocrine gland. Most persons know the pain that must be endured when the old path is abandoned.

A number of writers have marvelled at the accuracy with which the appetite meets the bodily needs, because the weight of most healthy adults scarcely changes from year to year. It is stated in a well-known textbook that a man 20 years old who weighs 75 Kg. will double his weight in another twenty years if he merely eats 1 butter pat (8.9 Gm. of fat) in excess of his caloric requirement every day. But the author apparently failed to take into account the enlarging surface area that accompanies increasing weight. Consider for example, a normal man who weighs 75 Kg. (165 lb.). He would be 5 feet 10 inches (178 cm.) tall, and his surface area would be 1.91 square meters. At age 20 his normal basal heat production would be 41 calories per square meter per hour. Accordingly, this hypothetic person would have a basal heat production of 1880 calories per twenty-four hours. If he consumed 80 calories a day in excess of his maintenance requirements, the resulting gain in weight would be accompanied by an increase in the area of his surface, which would become 1.98 square meters when his weight had reached 81 Kg. The corresponding normal basal metabolism would now be 1956 calories per twenty-four hours, instead of 1880 calories. The calories yielded by the extra butter fat would then merely furnish the heat of the increment in basal metabolism, and the subject would no longer store fat unless he made another addition to his diet. The solid line in Figure 36 shows the lessening gain in weight corresponding to the increasing surface area.[8] The broken lines indicate the rate at which weight would be added in the first and in the fifth year. Figure 37 shows how the diet would have to be progressively increased in order to permit the subject to continue to add to his weight at the rate at which he did so during the early weeks when the forbidden butter pat was actually furnishing 80 calories in excess of his requirement. By the time the man had doubled his weight, he would have increased his diet by 990 calories, not 80.

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* There are a number of recorded instances of rapid gain in weight in hypothalamic disorders caused by encephalitis in which there is no reason to attribute the increased appetite and resulting obesity to habit or anticipation of pleasure. An example is case 2 in the paper by Willder, Smith, and Sondejord, *Ann. Int. Med.* 6:724, 1932. *(Editors.)*

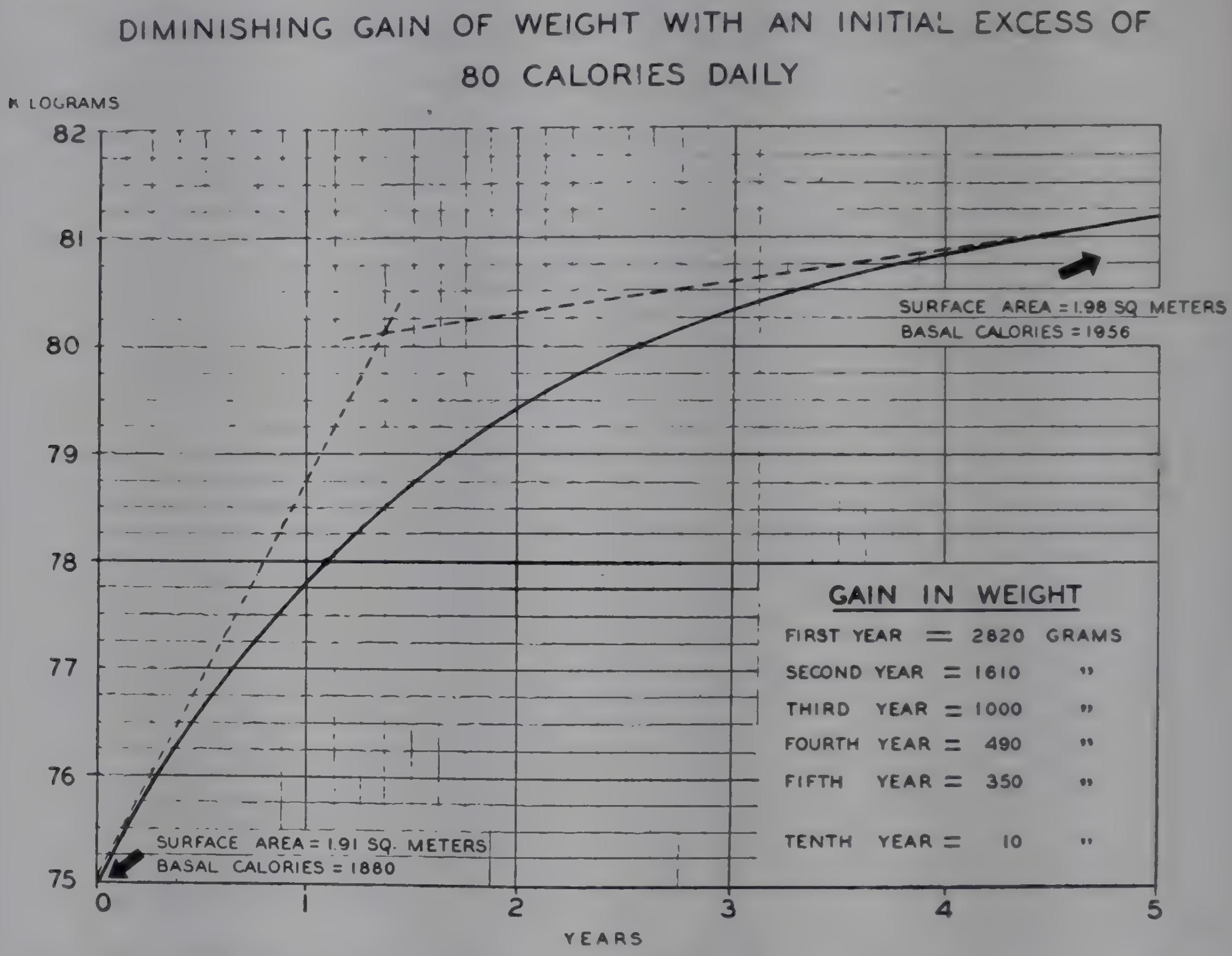

FIG. 36. Weight plotted against time, with an initial dietary excess of 80 calories per day.

These calculations assume that the activity of the subject remains constant through the years and that the added weight does not lessen his efficiency.

INACCURACY OF APPETITE

Harrington[25] has been interested in the inaccuracies of the appetite. She has devised experiments that test its capacity to supply a subject with the right number of calories when he is offered different types of food. Three meals a day were served, and more food was offered than was consumed. The subjects were asked to eat as much as they desired, but they were given no information about the composition of the diets, all of which were adequate. The standard diet contained 1.5 to 2 calories per gram. A bulky diet was prepared by omitting concentrated foods and emphasizing fruits and vegetables. It contained 1 calorie per gram. All subjects lost weight while taking it, because they ate only their habitual volume of food. The concentrated diet was constructed by substituting cream and butter for the milk of the standard diet and by increasing the sugar. It yielded 2.5 calories per gram. All subjects gained weight. They enjoyed this diet to the extent of eating more of it than was needed to satisfy the physiologic demands.

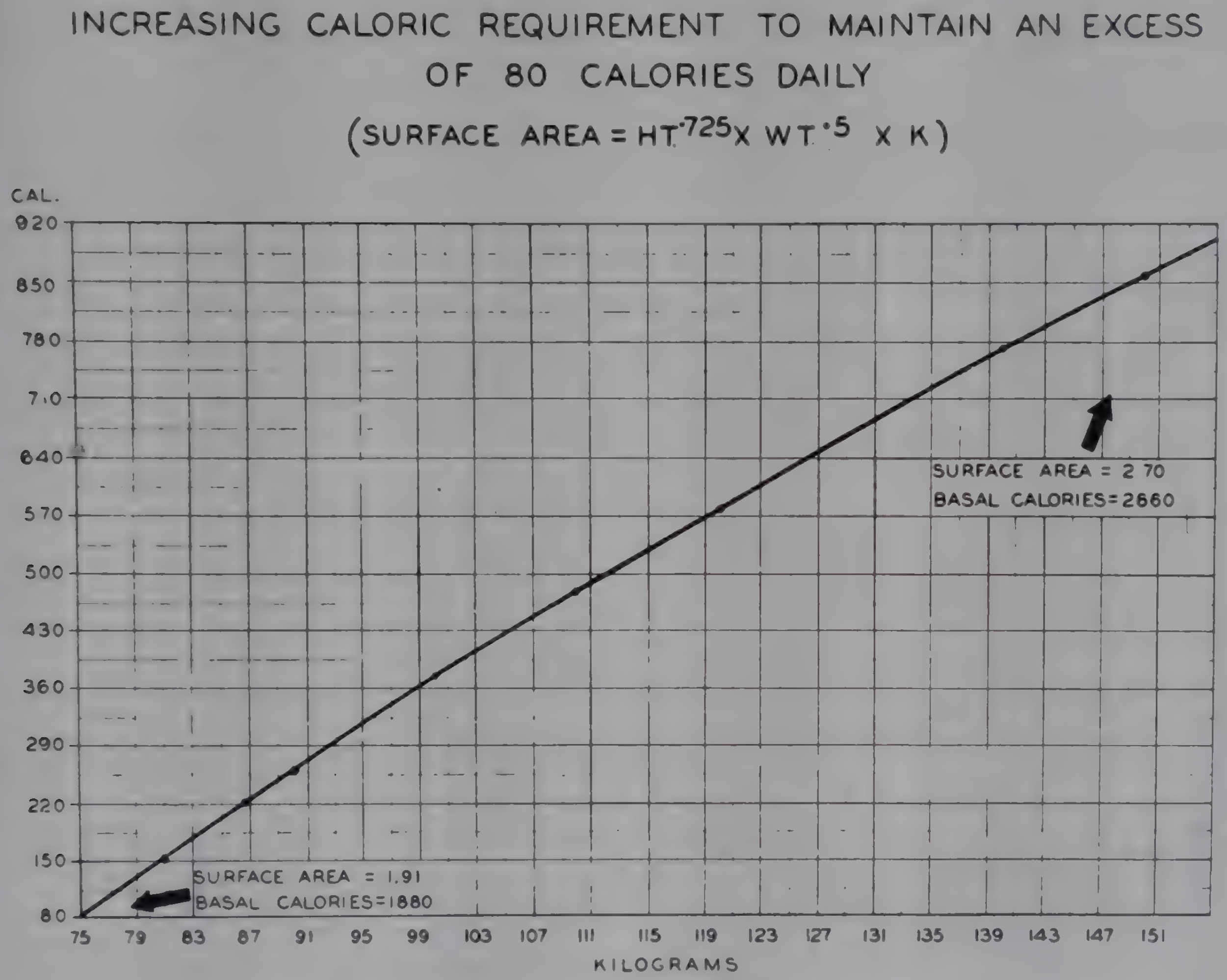

FIG. 37. Excess calories plotted against weight.

The matronly figure is not an unavoidable, although a common, sequel to the menopause. It does not mean that the secretions of the sex glands, now in abeyance, formerly had the power to restrain the growth of the adipose tissues. Rather does it indicate that the woman has reached that stage of life when she needs to strive less and finds more time for leisure. Even though she now needs much less food, she has more time in which to enjoy it and feels that she has earned the right to indulge herself. Probably she does not know or is but dimly aware that the candies she nibbles at the bridge parties which she so enjoys now that she is rested are adding their quota to her girth. Or if she is aware of the facts, she does not resist gain in weight, since the friends in whom she has the greatest confidence have assured her that nature intends her to lay on weight at this time of life. At first she still recognizes the signals that notify her that she has had enough to eat, but she deliberately ignores them because she has "toed the mark" long enough and from now on she is going to "humor herself." Gradually, the warnings become so blunted that she continues to enjoy gustatory pleasures until they are finally displaced by the discomforts attendant on ingestion of great excesses of food.

Emotional Craving for Food

Other people grow fat because life has become more difficult for them, not less so. They are persons who are struggling with a problem—sexual, social or financial—for which they can find no solution. But they have discovered that they obtain temporary solace in eating. For them food acts as a balm, as alcohol does for others who find life too hard. We have seen many obese patients who either deliberately or without being aware of the situation have turned to food as a means of relieving pent-up emotions. The following case history is a good example of the development of obesity in a patient who strove to lessen the pain of overwhelming disappointment by incessant eating.

The patient was an unmarried woman aged 41, 5 feet 4½ inches (164 cm.) tall, who weighed 225 lb. (102 Kg.) when she entered the clinic. When she was 25 years of age she found herself deeply in love with a young man, but her father was firmly opposed to their marriage. During the next six months she battled with the problem whether she should obey her father, whose guidance she respected, or should disregard him. She finally decided in favor of the father. By this time she had become so disturbed emotionally that she could not bring herself to face the world. In order to avoid contacts, she refused to leave the second floor of her home for four years and remained in bed most of the time. She gave no thought to the food that was brought to her by a servant except that she was aware of eating a great deal of sugar. The emotional instability became less marked after a time, and then she began to realize that she was causing her parents great pain and that she must once again take up the usual mode of life. At the beginning of the period of isolation she weighed 117 lb. (53 Kg.). When she emerged, her weight was 161 lb. (73 Kg.). She then went to a doctor for reduction of weight. He gave her a diet and 2 grains (0.13 Gm.) of thyroid daily. In less than a year her weight had diminished to 125 lb. (57 Kg.). Her father died suddenly shortly thereafter. At that time the family lived in a large house which they had previously been able to maintain generously, including the employment of servants. The patient now suddenly discovered that the family finances were in a precarious condition, and she decided that she must do all the work in the house. Even though there were only her mother and herself at home, she began her work at 4 o'clock in the morning and attempted to do all of the cleaning, cooking, and laundering. She shortly found herself overwhelmed with fatigue, and the fear that she would be unable to continue the work caused her to attempt to gain strength by eating a great deal. Soon she disregarded the regular meal hours and ate whenever she felt exhausted. She continued to struggle on in this way for about a year, when her weight had reached 177 lb. (80 Kg.). And now she had to admit to herself that the large amount of food she had been eating had not helped her. In fact, she fatigued more easily than before and was hampered by shortness of breath. But she was chiefly disappointed because the obesity disfigured her. She tried to reduce her weight (without the aid of a physician), but she continued to gain nevertheless. When she realized that she was failing again, she became tense and restless and was harassed by insomnia. It seemed useless to make any further effort. Since she could calm herself temporarily by eating, she no longer resisted and ate whenever she felt distracted. She gained 50 lb. (23 Kg.) in less than a year. Then she concluded to make one more attempt to reduce her weight and came to the hospital for that purpose.

The examination disclosed no abnormalities other than the adiposity. She was instructed to eat all her meals in the special diet kitchen, where she received 450 calories daily. During the next four months she lost approximately 60 lb. (27 Kg.). After she adhered to the diet for a few weeks, the craving for food had disappeared and her appetite was satisfied. She was amazed.

About a month later she became emotionally upset and experienced a distaste for food. For a time she refused a good deal of the diet, but this episode lasted only a few days. Subsequently she adhered strictly to the plan and had no desire to eat more than she was offered. Accompanying the conviction that her weight would soon be normal again, a change in attitude occurred. She no longer worried and found that she was calm and philosophic.

The next case is another typical example of the use of huge quantities of food to assuage a seemingly hopeless situation. This time it was the physical and mental cruelty inflicted by a drunken husband.

The patient was 25 years of age when she entered the clinic. Her height was 5 feet 7½ inches (171 cm.) and she weighed 248 lb. (113 Kg.). She had been married six years previously to a man who was apparently a successful innkeeper. The first three years of married life were peaceful and pleasurable. Then, for no reasons evident to the patient, the husband began drinking heavily, took to gambling, neglected his business, and went into debt. He became ill-humored and rough. To increase his income he converted the inn into a brothel and demanded that his wife, who was one of the waitresses, permit the male patrons to have sexual intercourse with her just as the other girls did. Her initial refusal was overcome by beating her so violently that she had to remain in bed for a week or two on numerous occasions to recover from the attacks.

She now noticed that for the first time in her life she was nervous and irritable and that she was annoyed by a gnawing sensation in her stomach. The latter discomfort was relieved by food, and she was gratified to find that large frequent meals made her better able to tolerate her lot. She now deliberately used food, wine, and whisky to comfort her. It was not unusual for her to eat three large steaks a day and fill in the intervals with almost continuous munching of anything that caught her eye, and she "washed down" the solid foods with generous draughts of beer, interspersed with frequent gulps of wine and whisky. At the beginning of this period of overeating she weighed 148 lb. (67 Kg.). This was normal for her. During the next two and one-half years she gained 100 lb. (45 Kg.). She was divorced at about that time and has not gained since.

The examination disclosed a slovenly, unkempt young woman who suffered great emotional pain as she revealed her cruel experiences. She expressed great gratitude and relief when she began to feel that we intended to treat her in a dignified manner, that we understood her problem, and that we were confident that we could make her a presentable young woman by reducing her weight to normal. She lost 17.1 lb. (8 Kg.) during the period of thirty-one days while she was an inpatient. She was discharged on a diet of 450 calories daily and has adhered to it without any difficulty.

Bruch[11] has made an exhaustive study of the food habits of 142 obese boys and girls, 2 to 13 years of age. She remarked that the tendency of the children and of their parents to minimize the food intake was encountered frequently but detailed questioning usually revealed the true picture. One mother, for example, who first answered, "Just normal, he doesn't eat much," later in the interview stated, "I know; I stuffed him like a goose." Nearly all the children had eaten excessive amounts of starchy food. She mentioned a boy of 10 who admitted six slices of bread as sandwiches, a piece of cake, four apples, and five bananas as a regular lunch, in addition to several glasses of milk. Not one child had learned to eat a mixed, well-balanced diet. Vegetables and salads were the foods most frequently disliked. All children ate between meals whenever they felt like it. Bruch was convinced that the children became fat in all cases because they over-ate. She emphasized the close association between overeating and the lack of social maturation. Many of the children, for example, were incapable of dressing themselves. It was not unusual to learn that a child of 10 years was still being dressed and bathed by the mother and was not allowed to play with other children. This overprotection, which deprives the child of normal outlets, turns his attention to the satisfaction gained by eating. The obesity in other children dated from an upsetting experience. Often the fear that sexual development was abnormal had given rise to self-pity and compensation in gluttony.

Hypoglycemia

It has been suspected that the hunger caused by hypoglycemia has driven some patients to overeat and so become obese. This idea seemed to be supported by the observations of a number of investigators who reported that the appetite of emaciated patients could be stimulated by injections of insulin. However, Freyberg,[18] who attempted to confirm these observations, found that the whole effect was obtained through suggestion, since injections of solution of sodium chloride increased the appetite as successfully as did insulin. Further, he found that insulin had no effect on appetite unless the patients were informed that the medicine was given to help them eat more.* Hypoglycemia is capable of causing great hunger in rats, but the level of blood sugar must be extremely low and continue so. MacKay and Callaway[32] were unable to make rats fat by injections of regular insulin. It was necessary to maintain continuous and severe hypoglycemia by means of large doses of protamine zinc insulin in order to obtain fat rats. The blood sugar was kept at such a low level that the rats died when deprived of food for four hours. Barnes and Keeton[2] found it necessary to inject huge doses of protamine zinc insulin to obtain obesity. When 32 units per kilogram was injected twice daily, some rats gained 3 to 4 Gm. daily. But food had to be kept before them at all times to prevent death. Even so, the mortality was high.

THE FUNDAMENTAL CAUSE OF OBESITY

Many investigators have striven earnestly to discover why human beings become obese. During the era when methods for measuring energy metabolism were being developed, several prominent investigators became convinced, first that the basal metabolism of obese persons was abnormally low, then that their caloric response to food was lessened. However, further study with better methods has demonstrated that the energy performances of the obese person in both these phases are normal. In fact, it is now known that the presence of adiposity increases the total heat production. A fat person requires more food calories than his normal control merely to avoid loss of weight.

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* Patients with insulomas very frequently become obese, and diabetic patients taking excessive doses of insulin frequently gain weight. *(Editors.)*

As the functions of the endocrine glands came to be understood and their key position was more clearly appreciated, it seemed to many leaders of the medical profession that hypofunction of the pituitary, the thyroid, or the gonads offered an adequate explanation of the development of adiposity. But again further study has shown that this is not the cause. *Luxuskonsumption*, lipophilia, and hypoglycemia have had the same fate.

These past efforts have not been wasted, however, for they have cleared the field for the acceptance of the doctrine that obesity is invariably caused by an inflow of energy that exceeds the outflow and that this disproportion is brought about by abnormality of the appetite. Excessive eating is an expression of a mood. It is a behavioristic response to a person's environment. This is not the place to attempt an analysis of behavior. It will be sufficient to state that conduct is an exceedingly complex blend of hereditary acquisitions modified by environmental experiences. This results in many different types of response by different persons when faced with seemingly identical problems. One person suddenly faced by danger will run from it; the next one will attack it. Physical fatigue causes an insistent desire for food in some persons; other persons suffering from fatigue are repelled by food.

While no attempt is made to discuss the ultimate origins of behavior, the understanding of obesity will be advanced by making a list of proximate causes to which some persons respond (in part) by overeating: (1) overemphasis by a parent on the importance of food in a child's upbringing; (2) gratification obtained from the flavors of foods; (3) the feeling of repose and comfort produced by a full stomach; (4) the temporary respite from anguish caused by intellectual, social, or sexual failure; (5) the food habits of youth which are carried over into middle age, even though the need for food is diminished; and (6) disabling disease with its lessened energy requirement which is compensated for by indulgence in food.

PREVENTION

Since obesity is an entirely preventable disease, people should be taught how to avoid it. A real effort to acquaint mothers with the dietary needs of their children would be a worthwhile addition to public health programs. School physicians ought to take the responsibility of teaching children the penalty of overeating. Physicians who are caring for patients suffering from chronic illnesses that limit activity should carefully plan the diet to avoid the insidious acquisition of excessive adipose tissue.

TREATMENT

Weight can always be reduced by adherence to a restricted diet, but cooperation by the patient is unlikely until the nature of obesity is elucidated and his particular reason for overeating has been discovered and explained to him. The chronicity of his ailment and its lack of immediately disabling features and of severe pain make it easy to find excuses for delaying treatment or for being lax about it. Most patients are unaware of the threat to life that obesity entails, and they can scarcely be expected to take their condition seriously until they acquire the information.

ENDOCRINE MEDICATION

Thyroid preparations are prescribed by physicians who attribute obesity to hypofunction of the thyroid gland, but it has been pointed out that the metabolic rate, with few exceptions, is normal and that the twenty-four–hour heat production of obese persons is greater than that of persons whose weight is normal. It does not seem wise to burden the patient with the irritability and nervousness of hyperthyroidism and to add to the burden of a circulation already overloaded. Only when the occasional patient is encountered whose basal metabolic rate is pathologically low is thyroid medication justified.

There is serious objection to the administration of any endocrine preparation because the patient, already conditioned by the propaganda of friends and of advertising, is confirmed in his belief that he is the victim of a glandular disease. He is satisfied that the substitution therapy will reduce his weight and that the diet, in spite of the preachments of the physician to the contrary, need not be taken seriously.

EXERCISE

Exercises of all sorts are widely advocated. These include massage and other passive exercises, but it surely must be realized that the muscular activity indulged in by the attendant is incapable of increasing the heat production of the patient. The latter must do the work if he is to dissipate the energy. But how much can be accomplished by muscular work? The mechanical equivalent of heat is 427 kilogram meters per calorie. Since a human being is only about 25 per cent efficient, he will dissipate 3 calories as heat for every calorie he converts to work. Accordingly, it will cost him 4 calories to raise 1000 lb. (454 Kg.) 3 feet (91 cm.). If he weighs 250 lb. (114 Kg.), he can climb a flight of stairs 10 feet (305 cm.) high at the expense of but 3 calories. But by depriving himself of one-third of a gram of butter or one-fourth of a teaspoon of sugar, he will reduce his intake 3 calories. He will have to climb 20 flights of stairs to rid himself of the energy contained in 1 slice of bread! If he is a good walker he may dissipate 100 calories per horizontal mile. Omission of an ounce of cream will reduce the inflow of calories to the same extent. Since adipose tissue yields 8 calories per gram, the mile's walk will reduce the patient's weight only 12.5 Gm. He must walk 36 miles (58 kilometers) to rid himself of 1 lb. (0.5 Kg.) of adipose tissue—how disappointing! Exercise is usually a much harder way of reducing weight than is limitation of food.

Patients who derive pleasure from being muscularly active need not be restricted, provided they are not overtaxing their hearts. Wilder[51] has recently pointed out that some obese patients lose weight more rapidly while they remain in bed than when they are up. He stated the suspicion that they are suffering from lesser grades of passive congestion due to myocardial weakness and that the rapid decline in weight when they are confined to bed is due to loss of edema. Unfortunately, those who enjoy the exercise are also often the ones who acquire a ravenous appetite in the process and find it harder to adhere to a diet when they are active than when they are quiet.

Exercise may be harmful in still another way. When low calorie diets are being used, most of the energy expended by the patient will be derived from body fat, and since the organism is restricted in its capacity to oxidize fat completely, this limit may be exceeded. Heat production of about 3500 calories per twenty-four hours in a person receiving a 450-calorie diet may be expected to cause acidosis. The pertinent facts in the most striking example of this condition that my associates and I have witnessed are recorded here:

Miss B., 24 years old and 5 feet 6½ inches (168 cm.) tall, weighed 289 lb. (131 Kg.) when she was admitted to the hospital for the treatment of obesity. During the next four weeks she was studied intensively on several reduction diets and was then placed on a diet that yielded 450 calories and consisted of protein 69 Gm., fat 10 Gm., and carbohydrate 30 Gm. Twenty days later, when her weight had fallen to 269 lb. (122 Kg.), she secured a room near the hospital but continued to come to the hospital for her diet. Since she enjoyed walking and knew that exercise would hasten the loss of weight, she strolled about considerably and gradually increased the length of the walks. One day she was on her feet, walking and shopping, for eight hours. Late that afternoon, for the first time, she felt fatigued and had no desire for food. Nevertheless, she continued her activities that evening. Next morning she had no complaints but refused most of the noon meal and all of the evening one. By 10:30 P.M. she was definitely nauseated. She drank some orange juice but vomited it. She slept well that night. The third day she had no desire for food and ate little. That evening she felt ill generally. The fourth and the fifth day she stayed in bed and ate nothing. By the sixth morning she was so nauseated that she vomited every time she ate. Her vision was blurred; she had a pain in the pit of the stomach, and she was short of breath. These symptoms increased during the day, especially the nausea. Then for the first time, she reported her difficulties to her physician, who moved her into the hospital and gave her an intravenous injection of 3000 cc. of a 5-per cent solution of dextrose in water. By the next morning she was still nauseated and fatigued, but the other symptoms were gone. Twenty-four hours later she felt quite well again.

DIET

There is a considerable difference of opinion about how many calories the reduction diet should contain. Some authors have expressed the opinion that patients are less liable to cheat when only moderate restriction is prescribed. Our own experience has led us to the opposite conclusion. The slow loss of weight that accompanies the more liberal plans is so discouraging that the patients often give up the diet after a few months.* We, like Evans,[16] have had most success when we have limited the calories sharply. The fear that the small diet will not maintain nitrogen balance has been set aside by Strang and McClugage.[47] They have shown that obese patients who subsisted on 450 calories daily were always in nitrogen balance when the diet contained 60 Gm. of protein. By choice, we prescribe a similar diet.

SELECTION OF FOOD†

In the instruction of an obese patient, it is a simple matter to teach him to omit sugar because sweet flavors are not easily disguised. It is also relatively simple to teach him to limit the use of foods high in starch. Restricting the intake of fat is a more difficult matter and requires special precautions in preparation and in cookery.

The foods commonly used in low caloric diets will be discussed here.

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* For a different philosophy, see Chapter 8, page 229. (*Editors.*)

† I am grateful to Frances MacKinnon for guidance in the preparation of this section.

Milk: half of a large can of evaporated milk has the same food value as a pint of fresh milk. A pint of skimmed milk or of buttermilk has half the caloric value of a pint of whole milk and is used for diets containing less than 1000 calories. Skimmed or separated milk obtained from the dairy contains only about 0.1 per cent fat. Pouring the cream layer from a bottle of milk will not give a product as low in fat as the dairy skimmed milk.

TABLE 43. FAT CONTENT PER 100 GM. OF VARIOUS FOODS*

0.1 to 2%	*2 to 5%*	*5 to 10%*	*10 to 15%*
Fish	Fish	Fish	Fish
Bass	Bluefish	Butterfish	Halibut, smoked
Carp	Halibut steak	Eel	Herring, canned
Cod	Mackerel, horse	Herring, Atlantic	Mackerel, Atlantic
Croaker		Lake trout	Mackerel, Spanish
Finnan haddie, smoked	Chicken	Salmon, canned	Salmon, Atlantic
Flounder, southern	Light meat	Shad	
Haddock	Dark meat		Lamb
Whiting	Gizzard	Duck, domestic	Chops
Perch	Liver	Muscle	Shoulder, lean
Pickerel			
Pike	Duck, wild	Turkey	Beef
Porgy	Muscle	Dark meat	Neck, very lean
Red snapper	Gizzard		Rib, very lean
Smelt		Rabbit, domestic	Roast, lean
Sole	Turkey	Muscle	Sirloin
Sturgeon	Light meat		Tenderloin
	Liver	Veal	Tongue, lean
Shellfish		Loin	
Clam	Rabbit, wild	Rib, lean	Venison
Crab	Muscle	Round, lean	Side and hind quarter
Crayfish		Rump, lean	
Frog legs	Veal		
Lobster	Kidney	Lamb	
Mussels	Liver	Leg, lean	
Oysters	Sweetbread		
Scallops	Tongue	Beef	
Shrimp		Brains	
	Lamb	Chuck, lean	
Miscellaneous	Liver	Corned beef, very lean	
Cottage cheese	Kidney	Dried beef	
Tripe		Foreshank	
	Beef	Hindshank	
	Liver	Kidney	
		Round, lean	
	Pork		
	Kidney	Venison, lean	
	Liver	Goose, muscle	
		Guinea hen	
		Quail	

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* Adapted from CHATFIELD, C., and ADAMS, G. Proximate composition of American food materials. Circular 549, U.S. Dept. of Agriculture, June, 1940. Articles high in fat have been omitted.

Meat and meat substitutes: beef, veal, lamb, and fowl are prepared by broiling, roasting, and boiling. Lean cuts should be selected. The fat content is determined by both the type of animal and the region of the body, as will be seen in Table 43. The methods used for preparing meat are suitable also for fish. Fat is removed from canned salmon or tuna by scalding it with boiling water. Since shell fish are lower than meats in calories, their use should be emphasized. Cottage cheese is the only cheese suitable for use in a diet with restricted calories; other varieties contain as high a percentage of fat as medium fat meat. Eggs should be boiled or poached to avoid the fat which is ordinarily used when they are fried or scrambled.

Vegetables (Table 44): for diets of 800 calories or less, the vegetables can be chosen only from the 3 per cent and the 6 per cent list. Because of their vitamin and mineral values the daily use of leaves, stems, or pods with a green color should be stressed. In the cooking or serving of vegetables it is usual to add some form of fat. Obese patients should be instructed that steaming, baking, or boiling vegetables in salted water are the only methods of preparation to be used and that the vegetables should be served without the addition of fat.

Fruit (Table 44): it is desirable to include two servings of low calorie fruits each day and preferably both should be eaten raw. Of the canned fruits, only those which are juice-packed or water-packed are suitable for use. In areas where housewives can their own fruit, it is a simple matter to add only water to the fresh fruits before the jars are processed. Contrary to popular opinion, a sugar syrup does not prevent spoilage of the fruit.

Bread: since bread is a concentrated food, none of it is included in the 450-calorie diet (Table 45) and only one slice is prescribed in the 600- and the 800-calorie diet (Tables 46 and 47).

Fats: it is important to instruct the patient carefully with regard to the amount of fat which is to be added to his food. For use in low calorie diets, there are some palatable butter substitutes which are calorie-free.

Other foods: since clear tea and coffee, mushrooms, and the soup made from bouillon cubes contain no calories, they can be used in any quantity desired. Saccharin is satisfactory as a sugar substitute. Salt, condiments, and vinegar may be used as seasoning.

Since it is believed that the epigastric distress of which many patients complain is due to emptiness of the stomach, it is important to consider the distribution of the food. Even though 3 meals a day may not always conform to the patient's previous food habits, he will find that he gets hungry less frequently if he eats at least 3 times a day. Protein requires several hours of gastric digestion and therefore slows the emptying time of the stomach. The use of a food high in protein at each meal, such as an

Table 44. FRUITS AND VEGETABLES CLASSIFIED ACCORDING TO THEIR AVERAGE CALORIFIC VALUES PER 100 GM.*

16 Calories "3 per cents" Carbohydrate, 3 Gm. Protein, 1 Gm.	*28 Calories* "6 per cents" Carbohydrate, 6 Gm. Protein, 1 Gm.	*40 Calories* "9 per cents" Carbohydrate, 9 Gm. Protein, 1 Gm.
Vegetables Asparagus Bamboo shoots Beans, green† Beans, wax† Bean sprouts Beet greens Broccoli Cabbage Cabbage, Chinese Cauliflower Celery Chard Chicory Cress, water Cucumbers Endive Escarole French endive Lettuce Mustard greens Radishes Sauerkraut Sorrel Spinach Squash, summer Tomatoes Tomato juice Turnip tops	Vegetables Carrots, canned Collards Dandelion greens Eggplant Kale Kohlrabi Leeks Lamb's quarters Okra Parsley Peppers Pumpkin Squash, winter Turnips	Vegetables Brussel sprouts Beets Carrots, fresh Onions, fresh Peas, canned† Rutabagas
Fruit Rhubarb	Fruits Blackberries Melons Strawberries	Fruits Applesauce, canned, unsweetened Apricots, water-packed Blueberries Cranberries Gooseberries Grapefruit Grapefruit Juice Peaches Pears Loganberries Limes Lemons Raspberries Tangerines

52 Calories "12 per cents" Carbohydrate, 12 Gm. Protein, 1 Gm.	*64 Calories* "15 per cents" Carbohydrate, 15 Gm. Protein, 1 Gm.	*96 Calories* "18 per cents" Carbohydrate, 18 Gm. Protein, 4 Gm.
Vegetables Lima beans, green, canned†	Vegetables Parsnips Kidney beans, red, canned† Peas, fresh†	Vegetables Corn, canned, sweet Potatoes
Fruits Apricots, fresh Cherries, sour, fresh Oranges Orange juice Pineapple Plums Kumquats	Fruits Huckleberries Grapes Mangos Nectarines	Fruits Prune juice Figs, fresh Grape juice Pomegranates

(For footnotes see opposite page.)

Table 45. REDUCTION DIET, 450 CALORIES

PROTEIN 60 GM., FAT 9 GM., AND CARBOHYDRATE 32 GM.

MENU PLAN	
Breakfast:	
6 per cent fruit	100 Gm.
Skimmed milk	200 Gm.
Coffee	Ad libitum
Luncheon:	
Meat or fish	60 Gm. cooked
3 per cent vegetable	100 Gm.
Skimmed milk	100 Gm.
Dinner:	
Meat or fish	90 Gm. cooked
3 per cent vegetable	100 Gm.
Skimmed milk	100 Gm.
SAMPLE MENU	
Breakfast:	
Melon	100 Gm.
Skimmed milk	200 Gm.
Coffee	Ad libitum
Luncheon:	
Boiled shrimp*	100 Gm.
Lettuce and tomato salad	100 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum
Dinner:	
Lean corned beef	90 Gm. cooked
String beans	60 Gm. cooked
Cole slaw (raw cabbage with vinegar and seasonings)	40 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum

* Note that 100 Gm. of shellfish has the caloric value of 60 Gm. of lean meat or fish.

egg for breakfast and meat, fish, or cottage cheese at luncheon and dinner, will keep the patient from having sharp hunger pains an hour or two after meals. If the meals are more than 4 hours apart, a quart of skimmed milk or buttermilk may be substituted for a pint of whole milk in the day's allowance and a glass of milk used at an interval halfway between each two meals and at bedtime.

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*Adapted from Chatfield, C., and Adams, G. Proximate composition of American food materials, Circular 549, U. S. Dept. of Agriculture, June, 1940.

Since tables like this were devised originally for use in prescribing diabetic diets, the foods are usually referred to in terms of the carbohydrate content. Thus any item in the first column is spoken of as a "3 per cent," not as a "16 caloric" food.

† The protein content of these foods is distinctly higher than 1 Gm. per cent. Accordingly, they should either be omitted when weighed diets are prescribed or the additional calories should be taken into account. Green beans and wax beans contain 2.5 per cent protein, canned peas 4 per cent protein, canned green lima beans 5 per cent protein, canned red kidney beans 6 per cent protein and fresh peas 7 per cent protein.

The matter of the measurement of portions calls for some comment. It is our experience that the use of dietetic scales, which weigh the food in grams or ounces, is the best solution for a trying problem. These scales are simple to use, and food may be weighed directly in serving dishes without the extra handling necessitated by the use of cups. The other and more commonly used method is prescribing foods in the ordinary household measure: cups, tablespoons, and teaspoons. For many cooked vegetables, such as greens, tomatoes, and diced root vegetables, measuring with a cup is satisfactory. For asparagus, broccoli, whole beets, or baked

TABLE 46. REDUCTION DIET, 600 CALORIES
PROTEIN 65 GM., FAT 9 GM., AND CARBOHYDRATE 65 GM.

MENU PLAN	
Breakfast:	
6 per cent fruit	100 Gm
Bread	30 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum
Luncheon:	
Meat or fish	60 Gm. cooked
3 per cent vegetable	100 Gm.
6 per cent fruit or vegetable	100 Gm.
Skimmed milk	200 Gm.
Dinner:	
Meat or fish	90 Gm. cooked
3 per cent vegetables	
1 raw	100 Gm.
1 cooked	100 Gm.
9 per cent fruit or vegetable	100 Gm
Milk	100 Gm.
Tea or coffee	Ad libitum
SAMPLE MENU	
Breakfast:	
Melon slices	100 Gm.
Bread, toasted, dry	30 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum
Luncheon:	
Cottage cheese with olives	90 Gm.
Head lettuce (dressed with tarragon vinegar and condiments)	100 Gm.
Raspberries	70 Gm.
Skimmed milk	200 Gm.
Dinner:	
Ground beef patty, broiled	100 Gm.
Beet greens with lemon	100 Gm. cooked
Sliced tomato	100 Gm.
Peaches, water-packed	100 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum

TABLE 47. REDUCTION DIET, 800 CALORIES

PROTEIN 73 GM., FAT 28 GM., AND CARBOHYDRATE 65 GM.

MENU PLAN

	Household measure	Weight (Gm.)
Breakfast:		
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Luncheon:		
Meat or fish	2 oz.	60
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Butter	1 teaspoon	5
Dinner:		
Meat or fish	3 oz.	90
3 per cent vegetables (1 raw, 1 cooked)	2 servings	200
9 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Butter	1 teaspoon	5
SAMPLE MENU		
Breakfast:		
Strawberries	½ cup	90
Poached egg	1	50
Whole wheat toast	1 slice	30
Butter	1 teaspoon	5
Black coffee	Ad libitum	Ad libitum
Luncheon:		
Crab meat salad:		
Diced celery	½ cup	60
Crab meat	½ cup	120
Minced onion and lemon		
Lettuce leaves		
Mayonnaise*	1 tablespoon	15
Melon	1	60
Skimmed milk	1 glass	200
Dinner:		
Beef steak, broiled	3 oz.	90
Asparagus	6 stalks	100
with butter	2 teaspoons	10
Lettuce salad:		
Lettuce	⅛ head	50
Tomato	1 small	100
Dressing*	Ad libitum	Ad libitum
Pear	½ cup	120
Skimmed milk	1 glass	200

*Ingredients: 1 egg, 1 teaspoon salt, 1 teaspoon mustard, 2 cups liquid petrolatum, 2 tablespoons vinegar, and teaspoon paprika.

squash, attempting to measure with a cup spoils the appearance of the vegetable. It is almost impossible to measure raw vegetables satisfactorily, and the use of terms such as "medium" or "small" is leaving the size of the portion to the patient's judgment. It is also difficult to describe the sizes of servings of raw fruits, although one may use the diameters of round fruits or number of berries or grapes. The greatest difficulty arises in teaching the patient the sizes or portions of meat. However, for diets of 800 calories or more, the use of household measures and descriptive terms may suffice. When diets with fewer calories are prescribed, the patient needs a dietetic scale to insure precision in measuring portions.

Diet Prescriptions

The plan for a diet restricted to 450 calories will be found in Table 45. It also shows the selection and distribution of the actual food for one day. It will be noted that green leaves and fruits are emphasized. The bulk thus afforded compensates partly for the meagerness of the diet, and, of equal importance, these foods are excellent sources of the vitamins. However, any possible insufficiency of vitamins should be guarded against by prescribing additional amounts of the vitamin B complex. The 400 Gm. of skimmed milk supplies nearly 0.5 Gm. of calcium, which is sufficient for an adult, and at the same time serves as a source of excellent protein. Practically all of the 60 Gm. of the protein prescribed is of animal origin. The fluid intake is not limited, since large amounts of liquid do not cause retention of water and restriction of fluids does not prevent it.

A diet of this type causes a loss of 3 to 5 pounds (1.3 to 2.3 Kg.) a week, on the average. The patient may be assured that he will lose 50 pounds (23 Kg.) in 3 or 4 months. After a few weeks, when he is convinced that he is really losing at the promised rate, he finds it less trying to continue the plan. It is harder to follow a diet at home than in the hospital where the food is put before the patient as a matter of course and without any expression of sympathy. This is especially true for the housewife who is responsible for feeding the family. The preparation of meals whets her appetite, and she must display great fortitude not to overstep her own meager allowance. For these reasons we urge the patients to experience the first 2 or 3 weeks of food restriction in the hospital. This also gives them the opportunity to acquire some information about the selection of food from the instruction provided for them.

A few patients whose circumstances require them to work hard physically claim that the 450-calorie diet reduces their strength so much that

TABLE 48. REDUCTION DIET, 1000 CALORIES

PROTEIN 75 GM., FAT 42 GM., AND CARBOHYDRATE 85 GM.

MENU PLAN	Household measure	Weight (Gm.)
Breakfast:		
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Coffee ad libitum, with milk	1 oz.	30
Luncheon:		
Lean meat, fish	2 oz.	60
Cottage cheese	3 oz.	90
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Bread	1 slice	30
Butter	1 teaspoon	5
Whole milk	1 glass	200
Dinner:		
Lean meat or fish	3 oz.	90
3 per cent vegetables (1 raw, 1 cooked)	2 servings	200
9 per cent fruit	1 serving	100
Whole milk	1 glass	200
Tea or coffee	Ad libitum	Ad libitum
SAMPLE MENU		
Breakfast:		
Strawberries	½ cup	100
Boiled egg	1	50
Whole wheat toast	1 slice	30
Butter	1 teaspoon	5
Coffee with milk	1 oz.	30
Luncheon:		
Cottage cheese	3 tablespoons	65
Kale	½ cup	100
Cabbage and celery salad	½ cup	100
Mineral oil dressing	1 tablespoon	15
Whole wheat bread	1 slice	30
Butter	1 teaspoon	5
Whole milk	1 glass	200
Dinner:		
Roast beef, fat trimmed	3 oz.	90
Broccoli	½ cup	100
Cucumber and radishes	¼ cup	50
Pear	1	125
Whole milk	1 glass	200
Black coffee	Ad libitum	Ad libitum

they cannot continue their occupations unless they get more to eat. When we are convinced that they have given the diet an honest trial and that they cannot be persuaded to continue it, some additional food is allowed. Often such patients can be satisfied with 600 calories arranged according to the plan in Table 46. Still other patients cannot be persuaded to adhere to a diet unless they are allowed 800 or even 1,000 calories (Tables 47, 48).

The treatment of obesity in children must emphasize behavior rather than diet. It has been pointed out that these children have not learned to obey and that often they are pampered and uncooperative. It is an integral part of the treatment to teach them to control their whims and desires and to help them develop a sense of proportion. The younger children need to be trained to eat food that is wholly adequate for them without reduction of the energy content much below the requirement of normal children of the same height and age. Sharp underfeeding may be too great a load when coupled with the correction of behavior. If the calories of the diet are adjusted to stop further gain in weight, the obesity will gradually disappear as height increases. Later on, when the child has become adjusted to the discipline, a further reduction in calories may be arranged if there is still much extra fat to be removed.

BIBLIOGRAPHY

1. ALBRIGHT, F., PARSON, W., and BLOOMBERG, E. Therapy of Cushing's syndrome. *J. Clin. Endocrinol.* 1:375, 1941.
2. BARNES, B. O., and KEETON, R. W. Experimental obesity. *Am. J. Physiol.* 129:P305, 1940.
3. BENEDICT, F. G., cited by LUSK, G., in *Physiol. Rev.* 1:523, 1921.
4. BENEDICT, F. G., and CARPENTER, T. M. Food Ingestion and Energy Transformations with Special Reference to the Stimulating Effect of Nutrients. Washington, Carnegie Inst. Pub. No. 261, 1918.
5. BENEDICT, F. G., and ROOT, H. F. Insensible perspiration: its relation to human physiology and pathology. *Arch. Int. Med.* 38:1, 1926.
6. BIGLER, J. A., HARDY, L. M., and SCOTT, H. V. Cryptorchidism treated with gonadotropic principles. *Am. J. Dis. Child.* 55:273, 1938.
7. BOLLMAN, J. L., MANN, F. C., and MAGATH, T. B. Studies on the physiology of the liver: XV., Effect of total removal of the liver on deaminization. *Am. J. Physiol.* 78:258, 1926.
8. BOOTHBY, W. M., and SANDIFORD, I. Summary of the basal metabolism data of subjects with especial reference to the normal standards for the estimation of the basal metabolic rate. *J. Biol. Chem.* 54:783. 1922.
9. BROWNE, D. The diagnosis of undescended testicle. *Brit. M. J.* 2:168. 1938.
10. BRUCH, H. Obesity in childhood: I., Physical growth and development in obese children. *Am. J. Dis. Child.* 58:457, 1939.
11. BRUCH, H. Obesity in childhood: III., Physiologic and psychologic aspects of food intake of obese children. *Am. J. Dis. Child.* 59:739, 1940.

12. Danforth, C. H. Hereditary adiposity in mice. *J. Heredity* 18:153, 1927.
13. Dock, W. The relative increase in metabolism of the liver and of other tissues during protein metabolism in the rat. *Am. J. Physiol.* 97:117, 1931.
14. Dublin, L. I., and Lotka, A. J. Length of Life. New York, Ronald, 1936.
15. Dürr, R. Über die Prüfung der spezifisch-dynamischen Eiweisswirkung in der Klinik. *Klin. Wchnschr.* 4:1496, 1925.
16. Evans, F. A. Treatment of obesity with low-calory diets: report of 121 additional cases. *Tr. A. Am. Physicians* 53:352, 1938.
17. Fisk, E. L. Health Building and Life Extension. New York, Macmillan, 1923.
18. Freyberg, R. H. A study of the value of insulin in undernutrition. *Am. J. M. Sc.* 190:28, 1935.
19. Freyberg, R. M., Barker, P. S., Newburgh, L. H., and Coller, F. A. Pituitary basophilism (Cushing's syndrome): Report of a verified case with discussion of differential diagnosis and treatment. *Arch. Int. Med.* 58:187, 1936.
20. Freyberg, R. H., and Newburgh, L. H. The obesity and energy exchange in a verified case of pituitary basophilism. *Arch. Int. Med.* 58:229, 1936.
21. Fröhlich, A. Wien, *Klin. Wchnschr.* 15:883, 1901.
22. Gaebler, O. H. Animal calorimetry: the specific dynamic action of meat in hypophysectomized dogs. *J. Biol. Chem.* 81:41, 1929.
23. Grafe, E. Metabolic Diseases and Their Treatment. Philadelphia, Lea & Febiger, 1933.
24. Grafe, E., and Graham, D. Über die Anpassungsfähigkeit des tierischen Organismus an überreichliche Nahrungszufuhr. *Ztschr. f. physiol. Chem.* 73:1, 1911.
25. Grafe, E., and Koch, R. Über den Einfluss langdauernder, starker Unternährung auf die Intensität der Verbrennungen im menschlichen Organismus. *Deutsches Arch. d. klin. Med.* 106:564, 1912.
26. Harrington, M. M. Appetite in relation to weight. *J. Am. Diet. A.* 6:101, 1930.
27. Hetényi, G. Untersuchungen über die Entstehung der Fettsucht. *Deutsches Arch. f. klin. Med.* 179:134, 1936.
28. Hetherington, A. W., and Ranson, S. W. Experimental hypothalamico-hypophyseal obesity in the rat. *Proc. Soc. Exper. Biol. & Med.* 41:465, 1939.
29. Jansen, W. H. Untersuchungen über Stickstoffbilanz bei kaloreinarmer Ernährung. *Deutsches Arch. f. klin. Med.* 124:1, 1917.
30. Johnston, M. W. The specific dynamic response to protein of individuals suffering from disease of the hypophysis. *J. Clin. Investigation* 11:437, 1932.

31. Lauter, S. Zur Genese der Fettsucht. *Deutsches Arch. f. klin. Med.* 150:315, 1926.
32. Lauter, S. Über die Beziehungen zwischen Energiehaushalt, Wasserhaushalt und Gewicht bei Fettsucht. *Klin. Wchnschr.* 5:1695, 1926.
33. Lusk, G. The specific dynamic action. *J. Nutrition* 3:519, 1931.
34. MacKay, E. M., and Callaway, J. W. Hyperalimentation in normal animals produced by protamine insulin. *Proc. Soc. Exper. Biol. & Med.* 36:406, 1937.
35. MacKay, E. M., and Sherrill, J. W. Influence of thyroidectomy on fat deposition in rat. *Endocrinology* 28:518, 1941.
36. Neuenschwander-Lemmer, N. Über Ausnutzungsversuche bei fettsüchtigen und normalen Menschen. *Ztschr. f. d. ges. exper. Med.* 99:394, 1936.
37. Newburgh, L. H., Johnston, M. W., Lashmet, F. H., and Sheldon, J. M. Further experiences with the measurement of heat production from insensible loss of weight. *J. Nutrition* 13:203, 1937.
38. Newman, H. H. Freeman, F. N., and Holzinger, K. J. Twins: A Study of Heredity and Environment. Chicago, University of Chicago Press, 1937.
39. von Noorden, C. Die Fettsucht. (2. Aufl.) Wien, Hölder, 1910.
40. Plaut, R. Gaswechseluntersuchungen bei Fettsucht und Hypophysenerkrankungen. *Deutsches Arch. f. klin. Med.* 139:285, 1922.
41. Plaut, R. Gaswechseluntersuchungen bei Fettsucht und Hypophysenerkrankungen: III., Mitteilung. *Deutsches Arch. f. klin. Med.* 142:266, 1923.
42. Plummer, W. A. Body weight in spontaneous myxedema. *Tr. Am. A. Study Goiter*, 1940, p. 88.
43. Ranson, S. W., Fisher, C., and Ingram, W. R. Adiposity and diabetes mellitus in a monkey with hypothalamic lesions. *Endocrinology* 23:175, 1938.
44. Schöndorff, R. Der Glykogenstoffwechsel der Weinbergschnecke (Helix pomatia) im Winterschlaf und beim Auskriechen. *Arch. f. d. ges. Physiol.* 146:151, 1912.
45. Smith, P. E. Relations of the activity of the pituitary and thyroid glands. *Harvey Lectures*, 1929-1930, p. 129.
46. Spence, A. W., and Scowen, E. F. Further demonstrations on hormone treatment of imperfect descent of testis. *Lancet* 2:983, 1938.
47. Strang, J. M., and Evans, F. A. The energy exchange in obesity. *J. Clin. Investigation* 6:277, 1928.
48. Strang, J. M., and McClugage, H. B. The specific dynamic action of food in abnormal states of nutrition. *Am. J. M. Sc.* 182:49, 1931.
49. Strang, J. M., McClugage, H. B., and Evans, F. A. The nitrogen balance during dietary correction of obesity. *Am. J. M. Sc.* 181:336, 1931.
50. Strouse, S., Wang, C. C., and Dye, M. Studies on the metabolism of obesity: II., Basal metabolism. *Arch. Int. Med.* 34:275, 1924.

51. von Verschuer, O. Die vererbungsbiologische Zwillingsforschung: ihre biologischen Grundlagen. *Ergebn. d. inn. Med. u. Kinderh.* 31:35, 1927.

52. Wilder, R. M., Smith, F. H., and Sandiford, I. Observations on obesity. *An. Int. Med.* 6:724, 1932.

53. Wiley, F. H., and Newburgh, L. H. An improved method for the determination of water balance. *J. Clin. Investigation* 10:723, 1931.

54. Wilhelmj, C. M., and Mann, F. C. The specific dynamic action of food. *S. Clin. North America,* 9:829, 1929.

55. Willson, D. M., Power, M. H., and Kepler, E. J. Alkalosis and low plasma protein in a case of Cushing's syndrome: a metabolic study. *J. Clin. Investigation* 19:701, 1940.

56. Zuntz, N. Einfluss chronischer Unternährung auf den Stoffwechsel. *Biochem. Ztschr.* 55:341, 1913.

Chapter 29

THE RELATION OF NUTRITION TO HEALTH

Frederick F. Tisdall

NUTRITION is considered by most physicians chiefly in relation to disease. In many medical schools, after teaching some of the principles of nutrition in the departments of biochemistry and physiology, the clinical material is limited to the so-called deficiency diseases, which constitute a very small portion of the average physician's practice. In contrast, very little attention is paid to the role of nutrition in the maintenance of health, a subject which should be of concern to everyone.

It is much more difficult to measure the effect of nutrition on health than it is to diagnose deficiency diseases or clinical signs of malnutrition. There are a number of indices of health but usually they can only be determined by observations carried on over a period of months or even years. Starting with the child, growth is an index of health. The rate of growth may vary all the way from the maximum inherent in the individual to no growth at all. Physical fitness, mental alertness, and resistance to many infections are also indices of health. These qualities can vary all the way from the maximum inherent in the individual to complete absence. If we add to these four indices of health the ability to produce healthy offspring, we then have a series of measurements which can be used in assessing the level of health of the individual. If the level of health is high, it is customary to speak of the individual as being in good health. If the level of health is low, he may be referred to as being in poor health although he is not suffering from any disease condition.

The state of nutrition is dependent not only on the food eaten but on many other factors, such as the absorption of nutrients from the intestinal tract, their storage, their rate of utilization, and their excretion. For instance, excessive peristalsis will interfere with absorption, disease of the liver cells with storage, thyrotoxicosis and fever with rate of utilization, and diabetes with excretion. The following discussion, however, is limited to the role of diet in nutrition and health. There is ample evidence that the average level of health today can be improved through better diet.

EFFECT OF NUTRITION ON GROWTH

It is hardly necessary to state that a lack of food will affect the rate of growth of the child. Recent studies of children in the liberated areas of Europe who had received an insufficient quantity of food for many months showed that their rate of growth in both height and weight was slower than that of comparable children receiving adequate quantities of food. What is frequently not realized is that, starting with a diet that is already clearly adequate according to ordinary standards, the diet may be so improved that an increased rate and amount of growth result. There is ample evidence that on the average the food consumed in Great Britain, the United States, and Canada during the past twenty-five years is better from the nutritional standpoint than that consumed in the preceding twenty-five years. There has been an increased per capita consumption of milk and milk products, vegetables, and fruits. The increased use of many foods in their raw state, as in salads, and the employment of better processing and cooking procedures have resulted in an increased supply of many nutrients, particularly some of the minerals and vitamins. Probably as a result of this improved intake, it is the rule rather than the exception to find the children of today taller and heavier than their parents. The records of University of Toronto freshmen[16] show that 1000 freshmen of an average age of 19 years examined in 1920-1921 had an average height of 5 feet, 8 inches and average weight of 138 pounds. Seventeen years later, in 1937, in a similar group of the same age, there was a gain in height of 1.5 inches, and a gain in weight of 5.2 pounds. Going back still earlier, the average suits of armor which were used in the sixteenth century would hardly accommodate a 15-year-old boy today.

Similar results were obtained in another study in Toronto,[10] when 78,000 Toronto school children were measured in 1939 and the measurements compared with those taken on 48,000 school children in 1923. The average child in Toronto in 1939 was the same height and weight as a child one and one-half years older in 1923; that is, at the age of 9.5 years in 1923 the school child of Toronto was the same height and weight as the 1939 Toronto school child at 8 years of age. Again this study furnishes indirect evidence that better nutrition affects the rate of growth.

Another study, which gives more direct evidence of the effect on rate of growth of the improvement of a diet already good, was conducted at this clinic on a group of children living in an orphanage.[19] The regular diet of the orphanage included amongst other things 24 ounces of milk daily, 1 ounce of butter, meat three to five times weekly, eggs 1 to 7 weekly, potatoes and one or two other vegetables daily, bread made from 72 per cent extraction flour, and some fruit, mostly apples, throughout the year. While the quantity cooking procedures employed did not differ from those usually used, we know from studies conducted on the feeding of the armed services during the last war that a considerable proportion of the water-soluble vitamins and minerals must have been lost in cooking.

Two groups of children were taken. One group continued on the regular diet of the institution and the other group, in addition to the regular diet, was given a vitamin B complex concentrate made from wheat germ and brewers' yeast. A small capsule weighing cnly 0.6 Gm. was administered daily to each child in this group. The rate of gain in weight of the control group was essentially the expected rate, while the children who received the additional vitamin B complex grew much faster. From this study one can conclude that, starting with a diet which is already clearly adequate according to ordinary standards, the diet may be so improved that the children grow larger than they otherwise would. Diet has a profound effect on growth.

EFFECT OF NUTRITION ON PHYSICAL FITNESS

Experience during and since the last war has borne in upon us the close relationship between food intake and physical fitness. It has been found that when insufficient food is available, production output decreases in direct proportion to the lack of food. In planning food rationing, this fact has been recognized and steps have been taken to ensure additional food for workers doing heavy manual work. Impairment of physical fitness develops in a matter of days when the individual receives insufficient calories. Studies conducted during the early years of the Second World War on Canadian service personnel fed various emergency rations gave surprising results. Small groups of seasoned troops on different rations carried out maneuvers each day involving severe physical exertion. At the end of four days one group which received only 2400 calories per man per day was so exhausted physically that the men were not a match for a group of 14-year-old boys. In contrast, those receiving 4000 calories per day were in perfect physical condition at the end of fourteen days.

However, it is not generally recognized that, even though a diet may ensure an adequate supply of calories, a moderate deficiency of any of the essential nutrients will impair the physical efficiency of the individual. Recent studies[2, 11, 23, 24] on the effect of an insufficient supply of members of the vitamin B complex on the capacity for physical work are striking. Individuals were placed on a diet low in thiamine—approximately 0.45 mg. per day (0.22 mg. per 1000 calories of the diet) in comparison with the *Recommended Dietary Allowance* of the Food and Nutrition Board of the National Research Council, Washington[17] of 1.5 mg. No evidence of beriberi developed. However, marked impairment occurred in the physical fitness of the individuals. When the thiamine intake was raised to 1.0 mg., the capacity for physical work was greatly increased. In other studies it was found that a lack of thiamine resulted in symptoms of lack of well-being, muscle pains, and moderate impairment of physical efficiency. A lack of the other members of the vitamin B complex was characterized by few symptoms but by marked impairment of capacity for hard work. Similar impairment of physical fitness[12] has been noted in individuals receiving a diet over a period of eight months which supplied approximately 10 mg. of ascorbic acid daily, an amount sufficient to prevent the development of any symptoms of scurvy but far below the *Recommended Dietary Allowance* of 75 mg. It is to be noted that in contrast to an insufficient supply of calories a lack of individual nutrients in the presence of an adequate supply of calories may continue for a matter of weeks or even months before signs of physical impairment become evident.

EFFECT OF NUTRITION ON MENTAL REACTIONS

It is extremely difficult to demonstrate the effect of diet on the mental development of humans. With animals, however, feeding a diet low in some of the essential nutrients for only the first few weeks of life markedly impaired their learning ability.[3, 4, 13] Newborn rats were nursed by mothers who were receiving a diet deficient in the vitamin B complex. By this procedure these newborn rats received a diet low in the vitamin B complex for the first four weeks of their lives. Other newborn rats were nursed by mothers receiving a perfect diet. After four weeks, all the newborn rats were weaned and given a perfect diet. While the rats which had received the diet that was deficient in the vitamin B complex did not gain as well as the control rats during the first four weeks of life, they then proceeded to grow and develop physically at the normal rate so that at 4 to 6 months of age, which corresponds to about 10 years of age in human life, the deficient rats were almost the same weight and had the same physical appearance as the control animals. However, when the rats were tested on their ability to learn to go through a maze, a marked difference in the performance of the two groups was noted. The control group learned to go through the maze on an average of 28 trials, while the vitamin B–deficient rats took 40 trials. Other measurements, such as the average time required, the average number of errors made, and the excess distance traveled, all indicated the same marked difference in the performance of the two groups. In other words, a lack of the vitamin B complex during the first four weeks of life of these rats, a period corresponding to the first two years in the human scale, impaired their ability to learn when they were at the comparable age of 10-year-old children in the human scale.

The effect of a poor diet on the mental outlook of individuals is marked. The lack of initiative of people receiving an insufficient amount of food has been amply demonstrated during and following the last war. During the studies on Canadian service personnel receiving an insufficient quantity of food, marked changes in their mental outlook were noted. They blamed their poor performance not on themselves but on their officers. They could see other groups of men who had received adequate diets marching vigorously along toward the end of each day's maneuvers while they could hardly drag one foot after the other. Their reaction was that the other men had cheated. Everything was wrong except themselves.

Recently a number of studies on humans have demonstrated that individuals on a low intake of thiamine become irritable and morose.[11, 23, 24] In a study of pregnant women,[8, 9] made in Toronto, women were observed who were receiving a diet low in a number of nutrients, including thiamine, calcium, and iron. The calorie intake was also somewhat below the desired level. When their diets were improved, the first change noted was an improvement in their mental outlook. Previously they worried about everything; housework bothered them; they were unhappy and slovenly in appearance. After three weeks on the improved diet they were much tidier, their faces were washed, and their hair brushed. They were obviously interested in their appearance. They were also much more cheerful.

EFFECT OF NUTRITION ON RESISTANCE TO INFECTION

There are many hundreds of references in the literature on the effect of diet on resistance to infection. One study[18] conducted at this clinic illustrates the relationship. Litter mates of rats were divided into two groups. One group received a diet which to the best of our knowledge was adequate except for the nutrient to be tested, which was completely absent. The litter-mates received the same diet but with additional amounts of the nutrient to be tested. In other words, animals in the latter group received an adequate diet. After the rats had been on these respective diets for four weeks, they were then given a measured amount of a disease-producing organism, *Salmonella muriotitis*, and the number of survivors was noted.

When the diet was deficient in vitamin A, 40 per cent of the animals survived compared to 79 per cent of those on an adequate diet. In another year, using different dosages, because the dosages had to be regulated very carefully (if too large a dose was given all the animals were killed; if too small a dose, they all survived), when the B complex was reduced, 20 per cent survived as compared to 72 per cent surviving when the diet was perfect. When vitamin D was lacking in the diet, 28 per cent survived as compared to 55 per cent of the litter-mates that were on the perfect diet. When the minerals were low, 54 per cent survived as compared to 87 per cent when the diet was perfect. When the animals got all their protein from sources other than animal protein, 40 per cent survived as compared to 90 per cent when there was some casein added to the diet. This study demonstrates that a low intake of a number of the vitamins, a low intake of minerals, and a change in the quality of the protein can all lower resistance to infection.

Almost invariably, poorly fed population groups have a high prevalence of tuberculosis. In Newfoundland, where in 1944 evidences of poor nutrition were found, the prevalence of tuberculosis was relatively high.[1] A similar relationship was found in the Canadian Bush Indian.[14] However, other etiologic factors probably are involved. A racial susceptibility to tuberculosis has been advanced as an explanation for its prevalence with certain aborigines. Attention has also been directed to the fact that very poor nutrition is accompanied by poverty, resultant poor sanitation, and poor housing. In Great Britain, during the Second World War, housing deteriorated markedly but nutrition was at a higher level than before the war. The prevalence of tuberculosis did not increase to any appreciable degree. In contrast, since the war, the Germans, who long were considered to have a racial resistance to tuberculosis, have suffered not only from poor housing but also from poor nutrition, and the incidence of tuberculosis has soared. Nutrition has a profound effect on resistance to infection.[*]

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[*] For a different conclusion see discussion on "Effects on Other Diseases" in Chapter 9. (*Editors.*)

EFFECT OF NUTRITION ON REPRODUCTION

It has long been recognized in animal husbandry that the health of a pregnant animal and its offspring is dependent in no small measure on the food eaten during pregnancy. Recently similar evidence has become available for the human from studies conducted in Canada, the United States, and Great Britain.[5, 6, 7, 8, 9, 15] In the Canadian investigation, the dietary habits of women coming to a large prenatal clinic in Toronto were studied. A record was kept of the amount of food eaten for a period of one week, and with this information the average daily intake of a number of nutrients was calculated. It was found that approximately one-half of the women attending this prenatal clinic were taking a diet which, according to our present standards, was not compatible with good health. Their average caloric intake was only 1600 to 1700 calories per day, in place of the recommended 2400 calories; their protein intake 55 Gm. per day in place of the recommended 85 Gm.; their thiamine intake 1 mg. per day, compared to the recommended 1.5 mg.; their calcium intake, only 0.5 Gm. instead of the recommended 1.5 Gm. per day; and an iron intake of 10 mg., in place of the recommended 15 mg. per day. The women with these inadequate diets were then divided into two groups, one called the Poor Diet Group, who were allowed to continue on their regular dietary intake, and the second, called the Supplemented-Good Diet Group, who were supplied with additional food. The daily amounts of the additional foods furnished each woman in this latter group were: milk, 30 oz.; canned tomatoes, 4.5 oz.; wheat germ with added reduced iron, 1 oz.; viosterol sufficient to furnish 2000 I.U. of vitamin D; 1 egg; 1 orange; and 1 oz. of cheese. These additional foods supplied each day 840 calories, 45 Gm. protein, 2.3 mg. of thiamine, 1.45 Gm. calcium, and 15 mg. iron. This raised their intake of the various nutrients to the level of the *Recommended Dietary Allowances*. The additional food was usually started during the fourth or fifth month of pregnancy. The women in both groups were carefully observed throughout pregnancy and any complications or abnormalities recorded. The obstetrician doing this recording did not know to which group the women belonged. During the latter stages of pregnancy, when subsequent dietary surveys were made, it was found that the diets of the Poor Diet Group had only slightly improved, the caloric intake having increased from 1600 to 1900 per day, the protein intake from 55 to 64 Gm. per day, the thiamine intake from 1 mg. to 1.2 mg. per day, the calcium intake from 0.5 to 0.7 Gm. per day, and the iron from 10 to 11 mg. per day. The group receiving the extra food had a daily intake of 2500 calories, 97 Gm.

protein, 3.3 mg. thiamine, 1.6 Gm. calcium, and 24 mg. iron. None of the women developed any signs of deficiency diseases.

The obstetricians gave a rating of the condition of the patients during the prenatal period, during labor, and during the postpartum period. The ratings during the prenatal period were based on the following: *good* indicated that the patient had progressed satisfactorily, *fair* indicated that minor complications had developed during the period of observation, *poor* meant that many or major complications had developed, while *bad* indicated that serious complications endangering the life of the mother, or resulting in the death of the baby, had occurred. The complications which affected the obstetrician's rating were severe anemia, preeclampsia and eclampsia, threatened miscarriage (any prenatal vaginal bleeding), accidental hemorrhage, severe vomiting, pyelitis, streptococcal vaginitis, and numerous minor complaints. Similar ratings were given for labor and postpartum convalescence. The major complications during labor were miscarriages, premature births, postpartum hemorrhage, long labor, primary uterine inertia, and the requirement of intravenous injection of fluid or transfusion. The complications during convalescence were severe anemia, pelvic inflammation, breast inflammation, cystitis or pyelitis, phlebitis, impetigo, embolism or thrombosis, and streptococcal vaginitis.

The results of this study were tabulated. The ratings were grouped into two division, those which were recorded as *fair* or *good* and those recorded as *poor* or *bad*. It is again emphasized that the obstetrician had no idea as to which group the women belonged at the time of their examination. It was found that 36 per cent of the women who had received a poor prenatal diet had a *poor* or *bad* prenatal rating as compared to only 9 per cent of the women who had received a good prenatal diet. Similar findings were obtained during labor and during convalescence. Twenty-four per cent of the mothers in the Poor Diet Group had a *poor* or *bad* record during labor, as compared to only 3 per cent of the mothers who had received a good prenatal diet. The average duration of labor for the primipara in the Poor Diet Group was 20.3 hours, as compared to the much shorter period of 15.2 hours for the women in the Supplemented-Good Diet Group. For the multipara, comparable figures were 11.1 and 9.5 hours. During the two weeks convalescent period, 11.5 per cent of the mothers in the Poor Diet Group had a *poor* or *bad* record as compared to only 3.5 per cent of the mothers who had received the good prenatal diet.

During the first two weeks of life, while in the hospital, 14 per cent of the babies from the mothers who had been poorly nourished had a *poor* or *bad* record, as compared to none from the mothers who had been well nourished.

For four weeks after the mothers left the hospital, the supplementary food was continued with the one group of mothers. As far as could be determined, the newborn infants received approximately the same care whether their mothers were in the Poor Diet Group or in the Supplemented-Good Diet Group. It is recognized that data of illnesses in the home during the first six months of life are not as accurate as desired, because they are dependent to a degree on the statements of the mothers themselves. The records indicate, however, that the babies from the mothers who had been poorly fed during the prenatal period were more subject to colds, bronchitis, pneumonia, and anemia than were the babies from the mothers who had been well fed during the prenatal period.

The most striking results of the whole study, however, were, first, that there were three and one-half times as many premature infants born to the mothers in the Poor Diet Group as to the mothers in the Supplemented-Good Diet Group, and, second, that 14 babies were lost, 7 from miscarriages, 4 from stillbirths, 2 from pneumonia, and 1 from prematurity, with every infant lost coming from a mother who had been poorly nourished during the prenatal period.

We thus have evidence that a diet good enough to prevent the development of any clinical entity or well-recognized disease condition can definitely affect the efficiency of the pregnant woman in producing healthy off-spring.

EFFECT OF NUTRITION ON LONGEVITY

We have defined the healthy individual as one whose rate of growth, physical fitness, mental alertness, resistance to infection, and ability to produce healthy offspring are at the maximum inherent in that individual. The effect of nutrition on these various indices of health have been discussed. However, in addition, we might expect the healthy well-nourished individual to live longer. Studies conducted with animals over many years have demonstrated this to be true.[20, 21, 22] Rats fed a diet consisting of a mixture of one-sixth dry whole milk and five-sixths ground whole wheat, table salt, and distilled water lived an average of 590 days, while rats that had the proportion of milk powder in the food increased to one-third lived an average of 654 days, or an increase of 10 per cent. It was also demonstrated that this increased longevity was because of a prolongation of the period of adult vitality. Further investigations indicated that the increased intake of calcium, vitamin A, and perhaps riboflavin, all contributed to the higher degree of health and the increased length of life. The significant conclusion is as follows: "Hence it may be regarded as established beyond any reasonable doubt that, starting with a diet which is already clearly adequate, it may still be possible to induce a very significant improvement in longevity by enriching the diet in certain of its chemical factors." Studies on many population groups throughout the world have demonstrated that poor nutrition is accompanied by early evidences of old age and by a shortening of the span of life.

The difficulty of measuring the level of health of a patient has been emphasized. In fact it might even be said that it is practically impossible to determine whether an individual is enjoying perfect health or not. However, it is abundantly evident that the physician's role must go far beyond the consideration of nutrition in relation to disease. Nutritional deficiencies which do not result in any well-marked clinical entities or signs of malnutrition can still affect the health and efficiency of the individual and thus create a problem which frequently only the physician can solve.

BIBLIOGRAPHY

1. Adamson, J. D., Jolliffe, N., Kruse, H. D., Lowry, O. H., Moore, P. E., Platt, B. S., Sebrell, W. H., Tice, J. W., Tisdall, F. F., Wilder, R. M., and Zamecnik, P. C. Medical survey of nutrition in Newfoundland. *Canad. M. A. J.* 52:227, 1945.
2. Barborka, C. J., Foltz, E. E., and Ivy, A. C. Relationship between vitamin B complex intake and work output in trained subjects. *J.A.M.A.* 122:717, 1943.
3. Bernhardt, K. S. The effect of vitamin B deficiency during nursing on subsequent learning in the rat. *J. Comp. Psychol.* 17:123, 1934.
4. Bernhardt, K. S., and Herbert, R. A further study of vitamin B deficiency and learning with rats. *J. Comp. Psychol.* 24:263, 1937.
5. Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C. The influence of nutrition during pregnancy upon the condition of the infant at birth. *J. Nutrition* 26:569, 1943.
6. Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C. Nutrition studies during pregnancy. *Am. J. Obst. & Gynec.* 46:38, 1943.
7. Ebbs, J. H., Brown, A., Tisdall, F. F., Moyle, W. J., and Bell, M. The influence of improved prenatal nutrition upon the infant. *Canad. M. A. J.* 46:6, 1942.
8. Ebbs, J. H., Scott, W. A., Tisdall, F. F., Moyle, W. J., and Bell, M. Nutrition in pregnancy. *Canad. M. A. J.* 46:1, 1942.
9. Ebbs, J. H., Tisdall, F. F., and Scott, W. A. The influence of prenatal diet on the mother and child. *J. Nutrition* 22:515, 1941.

10. A Height and Weight Survey of Toronto Elementary School Children. Dept. of Trade and Commerce, Dominion Bureau of Statistics, Social Analysis Bch., Ottawa, Canada, 1942.

11. Johnson, R. E., Darling, R. C., Forbes, W. H., Brouha, L., and Graybiel, A. The effect of a diet deficient in part of the vitamin B Complex upon men doing manual labour. *J. Nutrition* 24:585, 1942.

12. Linghorne, W. J., McIntosh, W. G., Tice, J. W., Tisdall, F. F., McCreary, J. F., Drake, T. G. H., Greaves, A. V., and Johnstone, W. M. The relation of ascorbic acid intake to gingivitis. *Canad. M. A. J.* 54:106, 1946.

13. Maurer, S., and Tsai, Loh Seng. Vitamin B deficiency and learning ability. *J. Comp. Psychol.* 11:51, 1930.

14. Moore, P. E., Kruse, H. D., Tisdall, F. F., and Corrigan, R. S. C. Medical survey of nutrition among the northern Manitoba Indians. *Canad. M. A. J.* 54:223, 1946.

15. People's League of Health, Report of Nutrition of expectant and nursing mothers. *Lancet* 2:10, 1942.

16. Porter, George D. Freshmen grow in stature. *University of Toronto Monthly*, December, 1937.

17. Recommended Dietary Allowances, Food and Nutrition Board, National Research Council, Washington. Reprint and Circular Series No. 129, October, 1948.

18. Robertson, E. C., and Tisdall, F. F. Nutrition and resistance to disease. *Canad. M. A. J.* 40:282, 1939.

19. Ross, J. R., and Summerfeldt, P. Value of increased supply of vitamin B_1 and iron in the diet of children. *Am. J. Dis. Child.* 49:1185, 1935.

20. Sherman, H. C., and Campbell, H. L. Further experiments on the influence of food upon longevity. *J. Nutrition* 2:415, 1930.

21. Sherman, H. C., and Campbell, H. L. Nutritional well being and length of life as influenced by different enrichments of an already adequate diet. *J. Nutrition* 14:609, 1937.

22. Sherman, H. C., Campbell, H. L., Udiljak, M., and Yarmolinsky, H. Vitamin A in relation to ageing and to length of life. *Proc. Nat. Acad. Sc.* 31:107–109, 1945.

23. Williams, R. D., Mason, H. L., Wilder, R. M., and Smith, B. F. Observations on induced thiamine (vitamin B_1) deficiency in man. *Arch. Int. Med.* 66:785, 1940.

24. Williams, R. D., Mason, H. L., and Wilder, R. M. Induced thiamine deficiency and the thiamine requirement of man: Further observations. *Arch. Int. Med.* 69:721, 1942.

25. Aykroyd, W. R., Jolliffe, N., Lowry, O. H., Moore, P. E., Sebrell, W. H., Shank, R. E., Tisdall, F. F., Wilder, R. M., and Zamecnik, P. C. Medical resurvey of nutrition in Newfoundland, 1948. *Canad. M. A. J.* 60:1, 1949.

Chapter 30

NUTRITION IN PUBLIC HEALTH PRACTICE

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DEVELOPMENT OF PUBLIC HEALTH NUTRITION PROGRAMS

Public health officials were first concerned with nutrition only as it related to problems of sanitation. The earliest federal action was taken in 1893 when Congress authorized the U. S. Public Health Service to establish sanitation regulations for common carriers engaged in interstate traffic. Public Health Service regulations for drinking water, issued in 1914, are the basis of standards now used in all the 48 states. Rules for sanitary service of food on interstate carriers were later added to the drinking water regulations so that, since 1921, interstate travelers have had the protection of federal rules governing the sanitation of all foods and beverages. Milk sanitation standards were first set by the Public Health Service in 1924. They have subsequently been revised and are now used in all parts of the country except New England and California.

Further federal control over the purity of food was authorized in 1906 by the Food and Drug Act. The Food and Drug Administration, with its powers expanded in 1938 by the passage of the Food, Drug, and Cosmetic Act, sets standards for food and drug products and enforces regulations pertaining to purity, adulteration and labeling.

The Department of Agriculture is another federal agency which has participated in the public health aspects of nutrition for many years. It is not only responsible for the inspection of meat, but also for a wide range of nutritional activities directed primarily to the rural population. Educational programs and other assistance is given to farmers on problems of food production, preservation and preparation. In the practical application of nutrition knowledge, this agency has continued to lead all others.

Programs of state and local agencies developed in much the same sequence as did the federal activities. Local responsibility for the nutritional welfare of its citizens began, in most places, with the establishment of standard water, milk, and food ordinances. Interest then extended to the purity of foods and drugs and many states set up their own control laboratories and conducted sanitary inspections of food and drug products.

In addition to governmental action in the field of nutrition, important contributions have also been made by food industry groups and by private organizations, associations, and foundations.

Although these early activities of official and voluntary groups had public health significance, the first specific public health approach to the problem is generally conceded to date from the pioneer work of Joseph Goldberger and his associates in the Public Health Service. They demonstrated in 1916 that pellagra was a dietary deficiency disease which could be prevented and treated by proper diet. This was a great medical discovery in that it revealed the cause of widespread disease but it was of even greater importance in clearly establishing the fact that public health practices could and should be applied to the solution of the nation's nutrition problems.

Since Goldberger's time, advances in nutrition knowledge have been rapid. The discovery of new dietary essentials, the recognition of new deficiency syndromes and symptoms, new laboratory procedures and newly recognized relationships between malnutrition, ill health, and poor development are some of the new findings. This is probably only the beginning. It is conservatively estimated that between 3000 and 4000 American scientists are currently engaged in investigations on food and nutrition. Large sums of money from both governmental and private foundation sources are invested in grants and fellowships for nutrition research. Even more extensive activity may be revealed when the Food and Nutrition Board of the National Research Council completes its survey and index of all nutrition research and research workers.

The rapidly increasing body of nutrition knowledge and the growing evidence that malnutrition is of real public health significance present both a challenge and an obligation to the health officer to carry on an adequate nutrition program. It recently has been recognized that even relatively mild malnutrition affects the health status of the individual. Although methods for recognizing and accurately measuring the early signs of nutritional failure are still being sought, we are aware that the problem is more prevalent than we once believed. The many nutrition surveys already conducted show that malnutrition is a large problem on the farm and in the city; in both children and adults; in all sections of the country. It is found among those who have all the money they need for food as well as among families with inadequate incomes. And while it is more common in low income groups and in certain sections of the country, no group or section is sufficiently free to warrant neglect of the problem by the health officer.

The problems of developing a practical, public health program, however, are many and difficult. The fact that relatively mild signs of malnutrition are so common and nonspecific has made many health officers reluctant to accept responsibility for dealing with malnutrition as they would deal with communicable disease control. The economic factors which are involved, the question of food availability, fixed food habits, and other considerations add to the complexity of the problem from a public health viewpoint.

Fortunately, improved technics are being steadily developed. The National Nutrition Conference held in 1941 furnished a blueprint for a nutrition program through the war and brought about a valuable coordination of nutrition activities. Many of the recommendations of that Conference are still applicable today. The dietary allowances recommended at that time by the Food and Nutrition Board of the National Research Council have become the standard for good nutrition. The council also gave sound scientific guidance to the Government's nutrition program. Under the impetus of patriotism, food rationing, increased industrial production, better incomes, home gardening, and other food-raising drives, public interest in nutrition was aroused.

While many of the wartime stimuli have disappeared, the experiences of that period have advanced the development of permanent programs. Because of high food costs, public interest in nutrition has continued into the postwar period. There is a real demand for health education—people are eager to learn how to eat to maintain health on less money. This interest can be constructively channeled, and an adequate nutrition program can be developed, only if health officials are clearly aware of the nutritional goals they wish to achieve.

OBJECTIVES OF A PUBLIC HEALTH NUTRITION PROGRAM

Ultimate objectives in all public health nutrition programs are twofold: (1) To prevent malnutrition by maintaining the best possible state of nutrition among the entire population; and (2) To attack all existing malnutrition.

The prevention of malnutrition is perhaps the most difficult of these two objectives. It involves intensive health education so that certain food habits are changed. It depends also upon the improvement and better distribution of food supplies. Adequate planning for emergencies such as flood, storm, drought, war, and economic depression must likewise be included in the long-range preventive program. All too often, at present, the nutritional problems which accompany disaster are neglected. Community planning, built around the canteen and disaster-feeding training programs already established by the American Red Cross, would assure victims and rescuers of more than a doughnut and coffee diet. And in terms of maintaining ability to resist disease, adequate nutrition is probably as important as inoculations and other preventive measures which have become routine procedures in the handling of emergencies.

Results of long-range preventive programs are slow, unspectacular, and difficult to measure. Given an opportunity, however, the value of maintaining good nutrition for everyone can be demonstrated in terms of lower mortality and morbidity rates as well as better growth and development of children.

Work toward the second objective—stamping out all existing malnutrition—yields results that are more rapid and visible and for that reason is likely to prove more popular and to secure more adequate support. An important prerequisite to the attainment of this goal, however, is the obtaining of accurate information on the prevalence and severity of nutritional deficiency diseases. To secure this data, we need to develop methods for assessing human nutrition which can be adopted by health departments. We also need to establish administrative patterns which can be used by state and local health departments to increase the efficiency of their public health programs.

However, in spite of handicaps due to lack of knowledge, we already know enough to make an effective public health attack on malnutrition. The pattern of local, State and Federal responsibility is likewise sufficiently developed to permit a quite specific outline of duties for all types of public health officials.

NUTRITIONAL RESPONSIBILITIES OF HEALTH DEPARTMENTS

Health officials have five principal types of duties to the public in relation to nutrition.

1. Practical Application of the Science of Nutrition to the Feeding of the Population

The use of food for health is a matter of immediate concern to the health officer and to each member of his department. The clinic physician, the public health nurse, and the nutritionist all should know something of the nutritional needs of the individuals they are treating.

Health departments should assist practicing physicians in arranging for a supply of mother's milk when necessary for premature babies and should provide dietary supplements in prenatal and infant clinics.

Public health officials should advise Boards of Education on school lunch programs and should initiate and give active support to legislative measures which will promote better nutrition for the population as a whole. They should strongly oppose trade barriers restricting the sale of foods that meet standards set by the Pure Food, Drug, and Cosmetic Act. They should advise legislative bodies when legislation for a sales tax on nonluxury foods is being contemplated.

Establishment and enforcement of standards for environmental sanitation, pasteurization of milk, and preservation of foods are other health department responsibilities which can be used to strengthen the nutrition program. Eventually, this type of activity might be expanded to include the setting up of standards for conserving the nutritional value of foods served in public eating places.

Conservation of grain and other foods through rodent-control programs and through health education activities designed to teach people to waste less food can also be considered as nutritional responsibilities of the health department.

2. Determination of Nutritional Status

The health department should be responsible for the nutritional status of the community in the same sense as it is responsible for the control of communicable diseases.

In most communities, serious nutritional deficiency diseases, while less prevalent than formerly, still occur more frequently than is often realized.

In addition to serious deficiency diseases, milder states such as rickets, simple goiter, obesity (particularly in adults), and underweight (in children) are prevalent in many areas of the country.

The basis for action programs to attack these problems is data accumulated from surveys and supported by clinical, dietary, and laboratory findings. Epidemiologic procedures similar to those used in the detection and control of goiter, mottled tooth enamel, dental caries, rickets, and pellagra should be studied and adapted to the discovery and prevention of other nutritional deficiency diseases.

The local health officer and his staff, if conscious of nutrition problems, can estimate the ones that are most important in his community. He and his assistants need not resort to complicated survey technics, but can obtain their essential data in the course of normal health department activities such as school health examinations and clinic services. Cooperation with the Red Cross, welfare, and other agencies concerned with nutrition will also yield valuable data.

3. Consultive Service to Those Working in Related Fields

Health officers have the responsibility of studying the impact of various social forces on the nutrition of the people. As appointed representatives of governmental authority, they should cooperate with others who are concerned with programs of a social, economic, or educational nature and, with the assistance of voluntary groups, work toward the correcting of conditions which lead to malnutrition.

The health department should be prepared to give consultive service on nutrition, as on other health subjects, to welfare agencies, hospitals, eleemosynary institutions, civic groups, food industries, educators, home economists, agriculturists, and others. This consultant service should include answers to such questions as: the incidence of malnutrition in the community, its nature, nutritive factors that are needed, and the quantities in which they are needed.

Such a consultive service can be a very important health department nutrition activity. It fills a real need and enables a small staff to assist in a variety of programs which reach a large number of people.

4. Nutrition Education as it Relates to Health

Furnishing nutrition information to the public is a primary responsibility of all health departments. If people are to improve their food habits, they must know what the body's physiologic requirements are and how to select foods to satisfy these requirements. The influence of food faddists and of misleading statements about foods can be best counteracted by an adequate program of nutrition information.

To be effective, educational material must be understandable to the ordinary citizen. It should stress the health importance of balanced meals and the deleterious effects of overeating as well as undereating. If a health educator is available, full use of his talents should be made in the preparation and distribution of the material. Furthermore, the nutrition education program of the health department, if it is to be successful, should take into account all the social aspects of nutrition, including family and regional food habits, religious restrictions, financial limitations, differences in educational status, personal aversions to certain foods, and the availability of foods in the particular locality.

The school lunch offers an excellent opportunity to teach nutrition to a group which is especially vulnerable to deficiency diseases. Lunch should be considered as a definite part of the school curriculum, being integrated with the home economics, natural science, and physical education courses. The boys, as well as the girls, should, through the program of lunch education, learn food preparation and develop habits of eating foods which make up a well-balanced diet.

5. The Health Aspects of Institutional Feeding Programs

Both local and state health departments have an opportunity to improve the nutritional status of institutional inmates. In many localities, supervision of the nutritional adequacy of institution diets is a stated responsibility of the health department. Even where the health department does not have such responsibility, the administrators of public institutions such as prisons, sanatoria, mental hospitals, homes for the aged, infirmaries, and orphanages may call on the health department for aid in maintaining adequate diets on limited budgets.

According to the 1940 census, almost a million and a half persons, about one out of every 100 Americans, are living in institutions. Many of them are suffering from malnutrition. The application of scientific principles of nutrition to the feeding of inmates of public institutions would not only improve their health but would probably bring about a substantial reduction in the amount of medical care which they require.

By competent and careful planning, it should be possible for the health official, working in cooperation with the director of public institutions in his area, to: (1) achieve nutritional sufficiency for inhabitants of these institutions through a planned dietary; (2) protect them from food or waterborne diseases through the use of proper sanitary engineering technics; and (3) reduce the cost of feeding by cutting down on waste and spoilage. It is essential that, in the feeding of institutionalized persons, the dietary selected in each case be adjusted to the nutritional status and the general state of health of the inmates, both as a group and individually. It is also important that the operation of the culinary unit in each institution be under the direction of a competent dietitian.

HEALTH DEPARTMENT NUTRITION PROGRAMS

Nutrition programs, if adequately carried out, should become an integral part of most other health department activities. For example, nutrition should be an important element of the tuberculosis control, school health, and maternal and child welfare programs. A good dental program requires nutrition service. The industrial hygiene program involves an interest in workmen's lunches and plant feeding programs. The sanitation service should include nutrition advice as well as sanitary inspection of eating places. Local health units and the nursing service need nutrition information. The control laboratory should be concerned with the vitamin content of various foods and medicines.

Thus it can be seen that nutrition cuts across practically the entire health department operation. For this reason, it requires an administrative position close to the state health officer himself and should be headed by a person with adequate training and experience in nutrition, public health practice, and medicine. The nutrition program must not be submerged in any one division of the health department. It must be an over-all service so that proper emphasis on nutrition can be given to all of the other health programs.

In focusing increased attention on nutrition in the health program, it is important for both state and local health officers to remember that they are newcomers to a field which has been tilled by many other organizations over a period of many years. That the health officer has a unique and needed contribution to make to the nutrition program is recognized by all groups, but he should not expect to "take over" as if he were embarking upon a totally new activity.

A brief consideration of the many aspects of a well-developed nutrition program will clearly indicate why the health officer will be helpless if he tries to develop his service without first learning the nature and extent of existing programs and integrating his work with them. Crop production, farm machinery and fertilizers, food distribution and transportation, food preservation methods, processing, and storage, are only a few of the many diverse factors involved in a comprehensive nutrition program. Educational and economic issues also affect the work. It is obvious that such problems cannot be solved by any one agency. Coordination and cooperative endeavor on the part of many voluntary and official groups is essential.

By his interest, leadership, and cooperation with others, the health officer can often stimulate extensive results with relatively little expenditure of funds. State nutrition committees, for example, were of great assistance to state health departments during the war. They should be continued and actively supported so that the state nutrition program can have the combined advice of experienced people in a variety of fields. In this way, an integrated plan can be devised, with each program strengthening all the others.

Nutrition education is one of the most valuable contributions made by these committees. This includes the production of literature prepared after joint consultation so that duplication of effort and the publication of conflicting advice are avoided. Other important educational functions are: promotion of food programs designed to improve nutrition; securing the universal use of iodized salt and of enriched flour, bread, and corn meal; and furthering the use of vitamin D milk as a preventive of rickets.

In addition to participating in existing programs, the health officer must find and develop that area of activity in nutrition work in which his help is most needed. Determination of the magnitude and nature of the health hazard involved in poor nutrition is, for example, a specific health department function. Development of a comprehensive public health nutrition plan, well organized and adequately staffed, is also his responsibility.

The epidemiologic approach can be applied to malnutrition just as it is to the control of venereal and other communicable diseases. It requires, however, a specially trained personnel as well as careful appraisal methods to determine extent, nature and incidence of the various deficiency diseases.

Other nutrition activities which seriously need the health department's assistance include:

Staff education not only of State, but also of local health department personnel. The field personnel in many health programs are certainly encountering nutrition problems. They should be trained to handle the minor problems themselves and to know when to call on the nutrition staff for assistance. They also need to be able to recognize when and how nutrition should be developed as a part of their own programs.

Aid to local units to meet specific problems such as rickets, pellagra, and anemia as well as general assistance, consultation, information, guidance, and encouragement.

Aid to other official and voluntary agencies such as institutions, relief, and welfare agencies, and educational systems and parent-teacher organizations that are concerned with teaching the importance of nutrition through school lunch and other school facilities.

Preparation of educational material such as leaflets, radio broadcasts, news releases, and exhibits. (Content of such material should be carefully planned so that it does not duplicate literature issued by other groups. Distribution shoud be carefully organized to produce maximum results.)

Service to the various divisions of the health department itself, particularly in connection with maternal and child health, dental hygiene, tuberculosis control, and industrial hygiene.

Work with physicians, through medical societies, in meeting requests for data on low-cost therapeutic diets and for diagnostic assistance in deficiency diseases.

Conduct of nutrition clinics for the diagnosis of deficiency diseases, to obtain data on prevalence, disseminate information on prevention, and to demonstrate the effectiveness of control measures.

Aid in organizing a State advisory committee to secure cooperation and integration of the many existing nutrition programs and to sponsor joint nutrition conferences, refresher courses, and workshops which bring new nutrition information to teachers and other nutrition workers.

These suggestions are not offered as a complete description of an adequate state health department nutrition program, but rather as a partial list of desirable activities, many of which could be started immediately in any state health department.

Choice of activities must, of course, be geared to local conditions, interests, and resources. Urban areas, for example, may wish to give special emphasis to nutrition in industrial hygiene programs. This can be done by promoting the provision of adequate eating facilities and serving of nutritious foods within industrial plants; distribution of nutrition information to workers; a study of each worker's food habits; and the inclusion of a thorough nutritional evaluation of each worker as a part of his regular or preemployment physical examination. Rural as well as urban communities should be interested in a program which emphasizes nutrition as a part of the school health program. School health examinations should include thorough nutritional appraisals, and the content of the school lunch should be adjusted to meet each child's requirements. Although the Federal Government's Office of Education and Department of Agriculture are authorized to administer the National School Lunch Program, its major purpose is the promotion of child health through improved nutrition. It is therefore the responsibility of the health department to see that the meals are planned to meet nutritional needs and that approved sanitary standards are observed in the local administration of the program. Nutritional programs in industrial plants and in schools should not be departmentalized, but should be considered as integral parts of the community-wide nutrition program.

State health departments which have a district-type organization should place the local nutrition services of each district under the direction of the health officer of the district. With the help of a district nutritionist, plans can be geared to local needs and local committees can be established so that, by utilizing volunteer services, effective local programs can be developed with small financial outlays.

A NATIONAL NUTRITION PROGRAM FOR HEALTH

Although this article deals with nutrition from the public health viewpoint, a nutrition program of national scope must be broad enough to include many closely related activities such as agriculture, food processing, enforcement of regulations, education, and welfare. Efforts of federal agencies responsible for such activities must therefore be unified through cooperative action. This was recognized during the war and many collaborative federal nutrition projects were carried out through a branch of the War Food Administration. After this agency was abolished, its coordinating functions were taken over by the Nutrition Programs Office of the Production and Marketing Administration of the U. S. Department of Agriculture. This Office, although deprived of its field staff, has continued to give over-all direction to the various state nutrition committees. Representatives from numerous agencies and groups interested in nutrition serve on these state committees.

Another postwar development resulting from the work of the War Food Administration is the Nutrition Planning Committee. Federal agencies that have field services and that are concerned with problems of food and nutrition are represented on this Committee. These agencies are the Office of Education, the Public Health Service, the Children's Bureau, the Bureau of Human Nutrition and Home Economics, the Extension Service, Farmer's Home Administration, American Red Cross, and the Nutrition Programs Office. The purpose of the Committee is to serve as a medium for the exchange of information on all federal activities in the field of nutrition. At present this Committee acts only in an advisory capacity. To devise suitable community nutrition programs, closer integration of the activities of the member agencies and increased influence on local efforts are needed.

Recognizing the need for increased federal participation in building adequate nutrition programs throughout the country, the Conference of

State and Territorial Health Officers recommended several years ago that the U. S. Public Health Service assist health departments by undertaking a program involving establishment of nutrition demonstrations, field investigations, and consultation services to state and local health units. This program was inaugurated in July, 1945, by the establishment of a Nutrition Section in the States Relations Division of the Bureau of State Services. Four mobile units, each containing laboratory facilities and each staffed originally with a physician,* a biochemist, a nutritionist, a public health nurse, a laboratory technician, and a clerk, were assigned to serve four geographic areas of the country, namely: New England, and the North Central, Southeastern, and Middle Atlantic States. The units have had five major objectives: (1) to test, develop, and apply methods which can be applied by health officers for assessing human nutrition; (2) to collect information on the prevalence of malnutrition; (3) to apply basic nutrition research to the field; (4) to collect information on the etiology and therapeusis of deficiency diseases particularly as it can be applied in the field; and (5) to conduct demonstration projects for training and educational purposes. More briefly stated, the purpose is to do field studies on the prevalence of nutritional deficiency disease from a medical public health standpoint and to test and develop remedial and preventive measures of practical value to public health organizations.

Another type of field program is being developed jointly by the Bureau of Human Nutrition and Home Economics of the U. S. Department of Agriculture and the Public Health Service. It involves studies of the relationships between human nutrition status and agricultural practices. Personnel from the Experiment Station of the Western Regional Office of the U. S. Department of Agriculture and a medical officer from the Public Health Service are conducting the studies under authorization provided by the Production and Marketing Act of 1947.

Other Public Health Service activities include the assignment of nutrition consultants to the District Offices of the Public Health Service and the assignment of medical officers to a few state health departments to assist in the development and expansion of state nutrition services.

It should be the aim of a National Nutrition Program to achieve coverage of the entire nation with nutrition services of some nature within a ten-year period. If this is to be accomplished, the prime requisites are additional funds and more trained personnel.

According to the 1948 annual report and plan of state and territorial health departments, approximately $534,188 has been budgeted for nutrition services for the current fiscal year. Of this sum, federal grants-in-aid account for $325,214. The U. S. Children's Bureau of the Federal Security Agency administers the major share of the federal funds now allocated for nutrition services. Increased grants-in-aid from the Public Health Service for nutrition work were requested at the Conference of State and Territorial Health Officers in December 1947. However, to finance an adequate program all sources of funds—local and state appropriations, federal grants-in-aid, and donations from private foundations—are necessary and more money is needed.

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* Reduction of funds later necessitated a reduction of the field staff in two of these units.

The need for increased personnel is also acute. According to their 1948 report, state and territorial health departments are currently employing a total of 156 nutritionists. All but one or two state health departments employ nonmedical nutritionists. Only two have a physician for full-time work on nutrition; another has a physician on a part-time consultant basis. The programs conducted by nutritionists consist primarily of health education and are chiefly directed to mothers and children. Little attention is being given to the nutritional needs of the public at large.

There does not seem to be any satisfactory basis for arriving at an accurate estimate of the personnel that would be needed to conduct more comprehensive nutrition programs. A suggested figure may be arrived at, however, from the report on local health units for the United States, prepared in 1945 by a subcommittee of the American Public Health Association's Committee on Administrative Practice. This report, which has been generally accepted as a sound basis for organizing health services in this country at the level of the local community, recommends that a minimum of about 1200 fully staffed local health units be set up to furnish complete health coverage for the inhabitants of the continental United States.

No specific mention of nutrition services is made in the report, but we may assume that adequate nutrition services probably can be furnished to local communities by the employment of one nutritionist for each 50,000 of the nation's population. During the initial stages of operation of the proposed local health unit system, however, each unit should employ at least one nutritionist, even if less than 50,000 persons are included within its administrative area.

Moreover, one nutrition supervisor should be appointed for each ten local nutritionists, if the plan proposed by the American Public Health Association is adopted, and each state health department should have on its central staff one physician trained in nutrition work, at least two nutritionists, and one biochemist. Total national requirements for nutrition personnel under this scheme, on the basis of the present population of the United States, would amount to approximately 50 physicians, 50 biochemists, and 3070 nutritionists.

Such a large number of nutrition personnel will not be available for some time to come. In fact, local health units are having increased difficulty in staffing even their traditional and well-established programs, as is indicated by a comparative survey which was recently completed in 12 states. In 1945, these states had 1257 vacancies in their departments whereas, in 1947, the number of vacancies had increased to a total of 1847. Under these circumstances, and in view of the fact that there are very few physicians trained in nutritional sciences who can organize and direct nutrition programs, local health departments have rightly given precedence to staffing their sanitation and communicable disease control programs.

However, despite this severe personnel shortage, health departments are not justified in ignoring their responsibilities in the nutrition field. Local health departments should cooperate to the fullest extent in community nutrition programs even though they cannot yet secure enough personnel to permit them to carry their real share of this work. Fortunately, the agricultural and home economics workers, who have carried practically all of the nutrition programs in this country for many years, are welcoming the belated interest of public health and medical authorities. The health officer will find valuable allies in the home economics and agriculture teachers in high schools and colleges. He will also find his work aided by the Agriculture Extension Service; the machinery of state nutrition committees; the American Red Cross; the Bureau of Human Nutrition and Home Economics of the U. S. Department of Agriculture; and the scientific foundations. Special reference should be made to the work of the home economists. It is in the schools of home economics that all dietitians and nutritionists received their undergraduate training. These schools have cooperated with medical, dental, and public health schools, and with various research institutions, in developing the fundamental concepts of nutritional science.

All of the above groups and individuals, as well as private physicians and medical schools, should be asked to assist in conducting nutrition programs. Their cooperation would not only make possible nutrition services to some areas of the country which now lack them, but should also reduce some of the overlapping of function and duplication of efforts which still exist in the nutrition field.

To increase the total supply of trained personnel, training in undergraduate medical schools, laboratories, and schools of home economics should be intensified. Arrangements should also be made to assign health officers to schools of public health, medical schools, and to hospitals for graduate training in nutrition science.

INTERNATIONAL ASPECTS OF A PUBLIC HEALTH NUTRITION PROGRAM

In planning both immediate and long-range nutrition programs, health officials must remain fully aware that the disturbances in food production and distribution due to the Second World War have created problems which may have far-reaching effects for many years. A comprehensive national program therefore requires attention to international food and nutrition problems and participation in their solution.

The importance of nutrition to world health, peace and prosperity was recognized in the creation of the Food and Agriculture Organization as the first international body created under the United Nations. Although nutrition as such is one of the primary concerns of FAO, its principal problems are in production and distribution. To be permanently successful, it must solve the difficult problem of getting food from so-called surplus areas distributed to deficit areas on a basis of need and regardless of economic or other barriers. This will require close cooperation with a section of the World Health Organization concerned with medical aspects of nutrition and deficiency diseases. This need is now clearly recognized and steps have already been taken to bring about the necessary liaison between the two agencies. The health and disease data of WHO will be essential to FAO, just as FAO data are essential to WHO in preventing and eradicating malnutrition. Other organizations doing valuable work on nutrition problems of international scope include the Pan American Sanitary Bureau and the Rockefeller Foundation.

All of these organizations are actively promoting better understanding among nations through their attempts to rehabilitate the agricultural systems and to build up the food resources of war stricken countries. Important work in maintaining minimum levels of nutritional adequacy among civilians of war devastated countries has also been performed by civil affairs and military government personnel. Many of the current concepts of nutritional requirements of individuals and of mass feeding are based on their experiences. Through these various international efforts, certain health precepts are gradually being established on a world-wide scale.

The award of research fellowships in the United States to foreign physicians and other nutrition specialists is another activity which fosters cooperation in the international attack upon malnutrition and helps many countries to meet their recognized need for organized nutrition programs. The provision and further extension of grants of this sort is a key point in the program of the United Nations and the Office of International Health Relations of the U. S. Public Health Service.

Extensive as is the present participation of the United States in the United Nations and other international programs, more should be done. We need a national nutrition committee of breadth, prestige, and power to plan and carry out our international policy and to adapt our national programs to international problems and national needs.

If we think of a complete nutrition service as one which covers all aspects of the problem, from the recognition of malnutrition to the provision of a food supply which is adequate for everyone, the answer is not in sight and there seems as little prospect of attaining it as there is of eradicating poverty. Nevertheless, our present rather haphazard and feeble efforts can be very materially improved.

We do not know, as yet, the extent or severity of deficiency diseases in the United States, nor have we perfected the organizational patterns, nor found the personnel necessary to provide the kind of nutrition service which will be required in a national emergency. Beginnings have already been made, however, in rectifying these and other deficiencies in our program of nutritional services and we are now in a position to advance more rapidly.

The content of the program must be flexible enough to shift with the changing world food picture, with new knowledge, and with changing ideas. We must always keep in mind the long-range, primary, idealistic goal of adequate nutrition for everyone.

Chapter 31

FOOD AND NUTRITION PROBLEMS ASSOCIATED WITH INDUSTRIAL WORK

Robert S. Goodhart and Maurice E. Shils

THE point has been emphasized repeatedly that the physician, whether in general or specialized practice, must familiarize himself with his patient's background, occupation, and environment in order to truly understand and fully help him. The physician-in-industry must understand and respect not only the situation within the plant but the individual's home and social environment. The development and growth of occupational medicine has been and continues to be along the path of analyzing, supervising, and treating the worker in terms of his total environment.

The need of a broad understanding of the field holds true in nutrition as it does in other branches of medicine. Nutrition involves much more than knowledge of the approximately forty nutrients known or believed to be essential for man. It embraces an understanding of how these nutrients function within the body, of how they are distributed in foods, how they withstand the vicissitudes of harvesting, distribution, storage, processing, cooking, and serving, of their availability to the individual, and of the effects of food habits, psychologic attitudes, and educational levels on persons whom we wish to see well nourished.

It is not hard to understand why there has developed special concern for the nutritional problems of workers, especially of industrial workers.

The nature and uncertainty of their employment, their educational, economic, and social status, and the problems of urbanization, make these workers as a group, together with their families, very vulnerable to food shortages, high food and other living costs, and poor dietary practices. In addition, the extent to which this country is industrialized makes eating-on-the-job a problem of tremendous proportions.[170]

Despite the many years that millions of our citizens have spent in the factories, comparatively little attention had been paid to how and what they ate until the Second World War. Even less attention had been paid to their nutritional status. The tremendous productive effort required by the recent war, combined with the manpower shortage, served to focus attention on this problem.

Previously, during the depression years of 1934–36, a study was made by the U. S. Department of Agriculture of the diets of families of employed wage earners in 43 industrial cities. The proportion of white families with diets classified as good ranged from 11 to 21 per cent in various geographic regions; those classified as poor ranged from 40 to 60 per cent.[165] In studies conducted in 1940 villages and 20 small cities,[134] it was found that only about one-seventh of the non-farm families in 1936 had diets meeting the National Research Council's original Recommended Dietary Allowances.[135]

Another survey conducted by the U. S. Department of Agriculture in the spring of 1942 indicated that increased incomes and widespread nutrition education had produced improvement in American food consumption patterns.[166] However, there was need for further improvement.

A subsequent survey[137] made by the Illinois State Health Department of 1102 luncheon trays in the cafeterias of four Chicago war plants revealed that only 8 per cent of the workers chose meals considered adequate by the nutritionists of the Department, 21 per cent chose meals considered to be borderline in adequacy, and 71 per cent purchased totally inadequate meals.[*] Another survey of the food selected by 1020 workers in a twenty-four-hour period was made by a nutritionist for a large industrial research foundation. It was found that 28 per cent of the workers had no milk with any meals, 22 per cent had no fruit, 44 per cent no eggs, 77 per cent no cereals, and 22 per cent no green vegetables.[137] It has been reported[164] that a number of war workers (10 per cent) in the San Francisco area often arrived at their work without breakfast; 64 per cent of the breakfasts chosen were rated as poor, and only 14 per cent as good.*

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[*] The meals served were scored according to the presence or absence of the following foodstuffs: 8-ounce glass of milk or two foods made from milk, each equivalent to one-half cup of milk; three-fourths cup of green or yellow vegetables; one medium or two small potatoes, one serving of meat, cheese, fish or eggs; two slices of whole-grain or enriched bread, one square of butter or fortified oleomargarine; and one of the following groups of foodstuffs: 4½ ounces of tomato juice, 4½ ounces of grapefruit juice or one half grapefruit, one orange, 4½ to 5 ounces of raw cabbage or green pepper or a mixture of the two. If all of the food items were selected, the luncheon was considered adequate. If one of the items was omitted, it was judged fair; and if more than one of the items was omitted, the luncheon was judged poor or inadequate.

In connection with surveys of food selection by industrial workers, particularly those utilizing the food-tray check, it must be pointed out that, although they are useful, they do not provide accurate information on the actual nutrient intake and are certainly unreliable indicators of nutritional status. They are inaccurate because food intake is only roughly estimated and because foods vary greatly in nutrient content, depending upon a number of factors such as origin, storage, and cooking practices. In addition, the food intake of a worker for one or two meals is not necessarily indicative of his over-all or usual food-intake. Future studies must go beyond the recording of food intake alone and must involve more clinical and laboratory observations on the nutritional status, health, and efficiency of the worker.

During 1941–1943, a combined study of dietary habits and nutritional status was conducted by Borsook and associates on aircraft workers in Southern California. Only 2 per cent had diets which met or approximated the Recommended Dietary Allowances[135] in all respects. Of 205 complete two-day diet records, the following percentages were found for which the amount of a specific nutrient was less than two-thirds of the Recommended Allowances: protein, 0.8 per cent; iron, 4 per cent; niacin, 7 per cent; thiamine, 14 per cent; vitamin A, 15 per cent; calcium, 25 per cent; riboflavin, 43 per cent; ascorbic acid, 46 per cent.[171] Young men had somewhat better diets than older men. Men under 25 years of age drank more milk and ate more citrus fruits than those 25 years or older, but they all consumed about the same amount of green and yellow vegetables and eggs. In connection with the apparent underconsumption of riboflavin and thiamine it must be remembered that the allowances for these factors have been reduced and recalculation would decrease the above percentages.

Prior to studying the effects of a vitamin-mineral capsule supplement, the workers were subjected to medical and laboratory examinations in order to determine their nutritional status.[11] Their weights, according to height and age were normal. Serum protein concentration was also

[*] The breakfasts were rated as good if the combination of foods included two of the following items: fruit, milk, cereal, ham or egg, and an additional food to supply 500 calories. A breakfast which had none of the above foods or supplied less than 300 calories was rated as poor. Persons who had no breakfast at all were rated in the "poor" class.

normal. Nearly every subject showed either gross or biomicroscopic thickening, opacity, or localized elevation of the conjunctiva, lesions which are considered by some to be due to vitamin A deficiency.[134] About 17 per cent showed one or more abnormal neurologic signs such as absence of knee and/or ankle jerks, calf muscle tenderness, plantar dysesthesia, loss of vibratory sensation in toes to a C-128 tuning fork, signs which may be indicative of thiamine deficiency. It was observed that about 26 per cent of the subjects had loss of vibratory sensation in toes to a C-256 tuning fork.

Signs associated with riboflavin deficiency were also found. Nine per cent showed cracks or fissures at the sides of the mouth and scaly, greasy desquamation at the angles of nose and eyes. From 23 to 43 per cent showed ocular symptoms such as lachrymation caused by light, eye fatigue or eye strain, burning, itchy, or gritty feeling in the eyes, and sensitivity to bright light. Niacin deficiency was reported in only 2 per cent. In 32 per cent plasma ascorbic acid concentrations were below 0.4 mg. per 100 ml., and another 20 per cent had plasma ascorbic acid levels below 0.6 mg. per 100 ml., indicating a low dietary intake of vitamin C. Hemoglobin values below 13.5 Gm. per 100 ml. were found in 11.6 per cent.

A rigorously controlled experiment on the effect of a "vitamin-mineral" supplement on their industrial efficiency was carried out on these workers.[10] The treatment period ran for a year, from March 1, 1942, to February 28, 1943, during which time the men received a vitamin-mineral supplement twice a day, five days a week. The daily supplement was composed of: vitamin A, 50,000 I.U.; vitamin D, 800 I.U.; thiamine, 10 mg.; riboflavin, 10 mg.; niacinamide, 100 mg.; ascorbic acid, 250 mg.; calcium (as carbonate), 500 mg.

After the workers had received the supplement for 9 to 12 months, they were again examined and the findings were reported.[12] No significant, specific, therapeutic effects of the vitamin-mineral supplement were observed on the various symptoms described above, with the possible exception of improvement in conjunctival transparency.

In spite of the paucity of demonstrable changes in the nonspecific anatomic signs of vitamin deficiencies, the vitamin-mineral supplement apparently did have some effect upon absenteeism, turnover, and general work performance (merit rating) of the participating workers (1173 at the beginning of the study and 595 at the end).[10, 13] In order to detect psychotherapeutic effects, one group was given the supplement, another was given a placebo, while a third group received no capsules of any kind. In the first six months the supplemented and placebo groups had similar absenteeism rates but the second six months showed a statistically significant reduction of 18.6 per cent in the supplemented over the placebo group. Interestingly, the reduction was greatest in unauthorized absences. The psychotherapeutic effect of giving pills was found to influence only absenteeism, to the extent of 29.3 per cent, an effect which persisted throughout the year in the reduction of illness absences. The vitamin-mineral supplement was found to reduce turnover by 26.9 per cent and the merit rating by 2.6 per cent. Although the last figure is the smallest, the actual gain from improved work performance is greatest since it applied to all workers, whereas absenteeism and turnover applied to only a fraction. It was estimated that the over-all gain to production from the physiologic effect alone of the supplement was 10.5 working days per man per year.

The relation of the vitamins to ability to perform muscular work and to psychomotor efficiency is discussed in more detail later in this chapter. Unfortunately, research of other investigators is not of a nature to deny or confirm the positive relation of the vitamins to attitude or morale in industrial situations that is suggested by Borsook *et al.* on aircraft workers.

NUTRITIONAL REQUIREMENTS FOR WORK

General

It may be stated at the outset that the overwhelming majority of male and female workers have nutritional requirements of the same order as those for individuals of the same sex and age in the general population. The investigations establishing our present knowledge of human needs are applicable to industrial workers, as are the Recommended Dietary Allowances of the National Research Council. However, there is need for an examination of the possible influences on nutritional requirements of various activities and stresses imposed in various occupations, in order to know whether any significant changes occur that demand alterations in dietary practices. Equally important is knowledge of the effects of nutritional deficiencies on the ability of workers to perform various physical tasks and to maintain adequate intellectual and psychomotor functions.

Calories

Despite the fact that caloric requirements engaged much of the attention of the early workers in quantitative nutrition and physiology and have been of continuing interest to succeeding investigators, our knowledge of this subject is still far from satisfactory. In times of prolonged food shortages precise information would be particularly important since under such conditions differential rationing has often been resorted to, with special attention being paid to the needs of industrial workers. Even in times of plentiful food supply, a knowledge of caloric requirements is valuable in institutional and mass feeding, such as the industrial cafeteria, because of problems of menu planning and purchasing.

The caloric requirements of individuals in various occupations vary from those of the sedentary workers, such as the draftsman or instrument maker who sits at the drawing board or work-bench most of his working hours, to those of the very active worker such as the logger in mountainous forest—a range of from less than 2400 to more than 6000 calories per day.

Burnet and Aykroyd[17] reporting for the Technical Commission of the Health Organization of the League of Nations in 1935 suggested an allowance of 2400 calories per day as adequate to meet the requirements of an adult male or female living an ordinary everyday life in a temperate climate and not engaged in manual work, with the following supplements for muscular activity: light work, up to 50 calories per hour of work; moderate work, from 50 to 100 calories per hour of work; hard work, from 100 to 200 calories per hour of work; and very hard work, 200 calories and over per hour of work. The Recommended Dietary Allowances of the Food and Nutrition Board call for 2400 calories per day for the sedentary male adult, increasing to 3000 calories for one engaged in moderate activity and to 4500 for the very active individual. Dill[36] has expressed levels of work in terms of the ratio of work metabolism to basal metabolism and defines moderate work as that in the range where the work metabolism is 1 to 3 times basal metabolism, and hard work as is in the range of 3 to 8 times. In the latter area lie most of the manual jobs in heavy industries, building trades, mining, and agriculture. Dill states: "We venture to say that, for the man doing hard work, a mean metabolic rate of about 8 times the BMR is as much as can be maintained for 8 hours."

There is a serious lack of information on the energy expenditure of many types of activity occurring in industry. Tables of energy requirements for the performance of certain occupations do exist, such as that compiled by Orr and Leitch[140] (Table 49), but the occupations which have been studied are limited and the definitions are almost entirely for the older "craft" type of work. Lacking are figures for the myriad of newer industrial activities such as the assembly-line worker in an automobile factory, the sandhog, the airplane mechanic, and the oil field worker. Adjustments of all early tables of requirements are necessary, also, to provide for advances in the mechanization of particular jobs within an occupation. It must be recognized that figures such as those given in Table 49 are merely approximations and that the requirements of the individual worker may vary greatly from the average for his occupation. To the factors of size, age, sex, and environment which affect caloric needs are added the variations due to relative efficiency of motion and differing activities on and off the job—all of which greatly influence the over-all caloric requirements.

TABLE 49. ENERGY REQUIRED IN THE PERFORMANCE OF CERTAIN OCCUPATIONS

CALCULATED ON AN EIGHT-HOUR WORKING DAY

	Occupation	*Calories*
KESTNER	Mental work	60
	Writing	120
	Carpenter	1440
	Stone mason	2640
	Sawing wood	3360
ROSE	Tailoring	400
	Typewriting	440
	Bookbinding	680
	Shoemaking	760
	Carpentry and metal working	1240
	Stone working	2520
	Sawing wood	3160
MOSS	Coal mining (avg.)	2460
MAISELS ET AL.	Coal mining—cutting	910
	Coal mining—hewing	1000
	Coal mining—timbering	1600
FARKAS AND GELDRICH	Tailoring	640
	Shoemaking	656
	Locksmith	936
	Joiner	1560
	Cartwright	1832
	Smith (heavy work)	2808
BECKER AND HAMALAINEN	Tailor	352
	Bookbinder	648
	Metal worker	1128
	Painter	1160
	Carpenter	1120
	Stone mason	2424
	Woodcutter	3104
FROIS	Riveting	2200

Modified from Orr and Leitch.[140]

During the last war the Food and Nutrition Board of the National Research Council considered the problem of the caloric requirements of industrial workers at the request of the War Food Administration, following the demand for extra amounts of rationed foods by workers in heavy industry.[62, 136] Recognizing the paucity of data on the requirements of occupational groups, the Board classified industrial workers into four categories for the purpose of differential allowances and stated: "While it may be desirable, for purposes of greater accuracy, to classify industrial workers into more categories than the four which have been chosen, for purposes of administrative action, a more detailed grouping would be too difficult to handle." The occupations included in the four categories are given in Table 50.

The body is capable of considerable adaptation, both physiologic and psychologic, to the level of caloric intake, and body weight can be stabilized at lower levels with moderately decreased caloric intake.[99, 130] Nevertheless from the practical feeding and production standpoints, the fact remains that workers engaged in activities requiring a large expenditure of energy cannot and will not continue such activities for more than a very short period of time unless they are supplied with adequate amounts of food. If the energy derived from food is diminished, they will expend less energy by doing less work. It has been shown experimentally that the work output of a fasting man engaged in hard work deteriorates considerably in two days.[24]

TABLE 50. CALORIC REQUIREMENTS OF INDUSTRIAL WORKERS
NATIONAL RESEARCH COUNCIL RECOMMENDATIONS

Category I: Over 5500 calories per day
- Loggers

Category II: Between 4500 and 5500 calories per day
- Coal and ore mining
- Foundry occupations including blast furnaces, steel works, and rolling mills
- Construction laborers, including contract and railway
- Longshoremen and stevedores

Category III: Between 3000 and 4500 calories per day
- Occupations in manufacturing of furniture and wood products including sawmill workers
- Occupations in production of petroleum and coal products
- Occupations in production of stone, clay and glass products
- Occupations in production of ships
- Metal-working occupations, including iron and steel and machinery
- Sailors and deckhands
- Transportation repair workers

Category IV: 3000 calories or less per day
- Occupations in processing of food products, except agriculture
- Occupations in processing of tobacco
- Occupations in manufacture of textiles
- Occupations in manufacture of fabricated textile products
- Occupations in printing
- Occupations in production of chemicals and chemical products
- Occupations in the production of rubber goods
- Occupations in the manufacture of leather and leather products
- Occupations in aircraft, automotive and railroad rolling stock industries
- Occupations in production of paper and paper goods
- Transportation occupations, except longshoremen, stevedores, sailors, deckhands
- Occupations in production of nonferrous metals and their products, except smelting and refining
- Miscellaneous

Johnson and Kark[91] have given the following description of the symptoms of severe caloric deficiency during hard work on the basis of experience with troops on experimental rations:

> With minor degrees of caloric deficiency besides unusual hunger, which is sometimes absent, physical disturbances appear. These are varied and consist of slight depression, with some loss of discipline and morale, irritability, disgruntlement, sullenness and lack of enthusiasm and vigor. Careful observation may reveal diminution of involuntary habitual motor activity, loss of spruceness, and general retardation of work output. As caloric deficiency increases, physical signs of disturbed function become more obvious. Fatigue, sluggishness, and lack of energy and drive develop, loss of muscular strength becomes apparent, and desire for rest, sleep and warmth increases. In some men slight tremors of the hand occur, and increasing grousing and quarrelsomeness. . . . At this stage there is also some weight loss and physical examination shows a marked decrease in motor activity of all kinds. . . . As deterioration in physical fitness and mental efficiency become more marked, dizziness, nausea, vomiting, weakness, exhaustion, collapse, gross apathy and involuntary sleep may occur. At this stage besides the obvious demoralization, weight loss is obvious and dehydration is present. The eyeballs are sunken, the mouth dry, and the lips parched and cracked. The breath smells strongly of acetone and neurological changes . . . may be found . . . physical fitness is "grossly impaired." . . . Symptomatic recovery from the early effects of caloric deficiency is usually dramatic after sufficient food and drink are consumed, and performance, energy, and morale can be restored to a high level within a matter of hours— Generally, however, men do not attain their former physical fitness until they have rested for some days or weeks on a normal diet.

In industrial situations, of course, enforced labor practices which would lead men to such physiologic and mental deterioration would not occur and would not be tolerated except under extreme emergency conditions. Rather, with restriction of caloric intake for any reason, work output would be curtailed accordingly. In experimental chronic semi-starvation in young men there has been found a marked impairment of the ability to perform hard work, an early and striking decrease in voluntary physical activity occurred and personality changes were common.[99] In this connection it is of some interest to note the productivity of German workers during the Second World War. Work output of workers in heavy industry was found to be directly related to caloric intake.[110] For example, young "cutters" in the coal mines had a daily output of 7.0 tons of coal per man on a total daily intake of 2800 calories, which was about 1200 calories above the estimated basal metabolic rate or about 170 calories per ton of coal mined. When 400 additional calories were allowed, output increased to 9.6 tons per man or 155 work calories per ton. At this rate the men lost, on the average, 1.2 Kg. of body weight in six weeks. The extra calories were raised to 800, whereupon the output increased to 10 tons per man and the body weight slowly returned to normal. Keys has recently reviewed various aspects of caloric undernutrition.[100]

Spacing and Frequency of Meals

Our custom of eating three meals a day is probably based more upon considerations of convenience than upon those of physiologic need. Experience in industry has shown the value to worker productivity of additional rest periods, particularly when associated with between-meal feedings. The view is widely held that between-meal snacks in themselves increase work performance and lessen fatigue. This may be true, but, unfortunately, there is no proof that frequent feedings increase physiologic capacity to perform work. Undoubtedly psychologic factors are important and account for some, if not all, of the beneficial results observed.

Haggard and Greenberg[68] found that high carbohydrate intake increased muscular efficiency in laboratory exercises on the bicycle ergometer and that variations in efficiency were correlated with the length of time between meals. They then carried on experiments with employees in a shoe factory, in which productivity was measured during periods when three or five meals per day were eaten, and concluded that five meals a day resulted in superior work performance (about 40 per cent increase in productivity). Unfortunately, the laboratory findings of Haggard and Greenberg do not agree with data obtained by other investigators and the reported changes in muscular efficiency have not been confirmed.[60, 70, 72] The study with shoe operators was not sufficiently well controlled to entirely rule out psychologic effects, as Ivy[83] has pointed out. These criticisms of course do not dispose of the finding that there was increased production with an increase in the number of meals. There have been similar reports[25, 69, 80] of improved efficiency or well-being with increased meals. However, the tests conducted in industry have not been sufficiently well planned to rule out the strong possibility that "morale" factors may have been predominantly responsible for the observed changes. In this connection, the observation of Borsook[10] that placebos had a marked and *prolonged* psychotherapeutic effect is noteworthy. The possibility also exists that an increased number of meals consisting of nutritious foods will improve the dietary of workers subsisting on inadequate diets and so improve health and performance.

Protein

Despite the fact that Liebig's theory that protein is the fuel of muscular work was disproved by Pettenkoffer and Voit in 1866, the suggestion is still occasionally made that persons doing hard work need increased proteins. Chittenden[22] in 1904 reported that men performed hard work and increased in vigor on a daily protein intake of 50 to 60 Gm. In 1926–27 it was again thoroughly demonstrated that in hard work there is only a small increase in nitrogen excretion, indicating little change in protein catabolism,[21, 22] and even that change may have been an indirect one.[59] One of the most recent experiments on man in this connection demonstrated that young men doing hard manual work over a period of two months accomplished as much and remained in as good physical condition with approximately 50 Gm. of protein daily as with approximately 160 Gm.[33]

CARBOHYDRATE AND FAT

The subject of the metabolism of sugar and fat in muscular work has likewise received much experimental attention and has been reviewed in detail on a number of occasions.[60, 98] While glucose has received wide publicity as the "quick-energy" sugar, the fact is that, normally, hydrolysis of both disaccharides such as sucrose and also the more complex carbohydrates takes place so rapidly in the digestive tract that differences between the rates of absorption and utilization of different sugars and starches are of no practical importance to the healthy individual. On the other hand, the view is held by many that a high-carbohydrate meal is conducive to the development within a short time of hypoglycemia with its attendant symptoms of hunger, weakness, and fatigue. A paper by Thorn and co-workers[162] on the reactions of a hospital patient to different types of breakfast has been widely quoted to support this view and as proof of the value of high protein meals in maintaining blood sugar level and a feeling of well-being. It is known that fat passes through the stomach more slowly than carbohydrate and that meals relatively high in fat and protein have a higher satiety value than those relatively low in these substances and high in carbohydrate; however, a recent series of papers by Haldi and his co-workers,[71, 72] Lundbaeck,[120] and others have challenged the acceptance of the idea of a hypoglycemic reaction as a normal response since no hypoglycemic responses were observed in a large number of healthy individuals following high-carbohydrate meals.

High-carbohydrate meals have been claimed to be beneficial when hard physical work is to be done and it is true that when maximal work is being performed a high carbohydrate intake allows the work to be carried on for a longer period than does a high-fat diet.[23, 24] It must be emphasized that this observation applies to continuous exhausting work of a type rarely met with in industry or everyday life. Although it has been found that carbohydrate is about 10 per cent more effective than fat as a fuel when the production of maximal work of some hours' duration is the criterion,[24, 111] in maximal work lasting only a few minutes or in light or moderate work prolonged for a matter of hours there is apparently little difference in the efficiency of diets of varying fat or carbohydrate content. In short-term maximal work such as short-distance speed swimming, Haldi and Wynn found no beneficial effect of high carbohydrate diets nor did they find that a high carbohydrate breakfast before exercise caused a hypoglycemic reaction.[21, 70]

Aside from their contributions to the palatability of foods and as carriers of fat-soluble vitamins and essential fatty acids, fats constitute the most concentrated form of food energy. This has practical importance for workers such as loggers who expend much energy, since they have the problem of ingesting a sufficient volume of food to meet their energy requirements. In these circumstances, unless fats are present in generous amounts, sheer bulk becomes a not inconsiderable factor in eating.

VITAMINS

The signs and symptoms of various vitamin deficiencies, the beneficial effects of therapy, and human requirements have been discussed in detail elsewhere in this volume. It suffices to mention briefly in this chapter the relation of vitamin intake to physical and mental efficiency and to resistance to various physiologic stresses which may occur in industry.

It must be borne in mind in considering the information given below that, although practically all experimental work on the relation of nutrition to fatigue employs physical stress to produce and measure fatigue, most modern industrial work fails to tax the physical endurance of the average industrial worker. The type of fatigue of greatest importance to industry is that involving the central nervous system, a type that has been the subject of very little scientific study.

The evidence leaves little room for doubt that the earliest symptoms of human deficiencies of those water-soluble vitamins (thiamine, niacin, and ascorbic acid) about which we know most are those of weakness, anorexia, irritability, and apathy. The ability to perform work efficiently is impaired in frank deficiency states, and adequate therapy will restore work capacity toward normal levels as will the adequate treatment of other types of illness where permanent incapacity is not involved.

VITAMIN SUPPLEMENTATION OF PRESUMABLY ADEQUATE DIETS

Simonson and co-workers[154] found no effect in five different types of muscular work from the addition of large amounts of the vitamin B complex to the usual diet of 12 healthy subjects. The vitamin B surplus did.

however, increase the fusion frequency of flicker, possibly a measure of central nervous system fatigue, in 8 of the 12 subjects, and all 12 subjects experienced subjective improvement of working capacity.

The thorough experiments of Keys and his group at the Laboratory of Physiological Hygiene at the University of Minnesota indicate no beneficial effect of supplementation with five B complex vitamins and ascorbic acid on the muscular ability of healthy young men on diets considered adequate, nor on their resistance to fatigue or recovery from exertion.[101] In experiments lasting ten to twelve weeks and utilizing normal young men it was found that intakes of thiamine at four different levels, from 0.23 mg. per 1000 calories daily up to 0.63 mg. per 1000 calories, exerted no beneficial effect on diets otherwise adequate. Muscular, neuromuscular, cardiovascular, psychomotor, and metabolic functions tested "were in no way limited —[and] clinical signs, subjective sensations and state of mind, and behavior were likewise unaffected."[102] A level of 0.96 mg. of thiamine per 1000 calories was allowed to the control subjects in these experiments.

Supplementation with B complex vitamins of a diet considered adequate did not increase the endurance of several subjects operating a bicycle ergometer.[4] The addition of 75 mg. of ascorbic acid to diets already adequately provided with this vitamin has been found to exert no detectable effects in terms of general well-being, physical vigor, and efficiency for hard work.[51, 90] Performance in three athletic tests was studied in two large groups of South African native miners subsisting on the usual compound diet. One group was given a daily supplement of orange juice containing 40 mg. of vitamin C and the tests were repeated at intervals over seven months. No differences were observed in ability to sprint 100 yards, run a mile, or put the shot.[95]

Frankau,[57] in a preliminary report which to our knowledge has never been amplified, stated that addition of nicotinamide alone or of nicotinamide and other vitamins to the diet of well-trained young men resulted in increased efficiency in carrying out tests involving both physical effort and coordination.

EFFECTS OF LOW NUTRIENT INTAKE ON EFFICIENCY

Consideration of this topic involves one in a highly complex subject characterized by conflicting evidence and opinion. Johnson *et al.*[89] found that young men subjected to hard daily physical work and subsisting on a diet deficient in members of the B complex, notably thiamine, exhibited symptoms of easy fatigability, apathy, muscle and joint pains, anorexia, and constipation and a marked deterioration in work performance within one week. Another group on the same diet supplemented with thiamine exhibited only a few mild subjective symptoms but their performance during hard work also deteriorated. Administration of yeast restored both groups to normal within four days.

Foltz, Barborka, and Ivy[50] studied the work performance on the bicycle ergometer of 4 medical students. When the thiamine intake was reduced from 0.43–0.59 mg. per 1000 calories of food to 0.33–0.38 mg. per 1000 calories, a decrease in appetite was noted within three weeks. After one month at this reduced thiamine intake a further decrease in thiamine intake was effected (0.17–0.21 mg. per 1000 calories) but no additional changes were noted until four weeks later, at which time a decided decrease in appetite and work output occurred, together with increased fatigue and muscle tenderness and a deterioration in mental attitude. The objective and subjective symptoms disappeared promptly after the addition of a yeast concentrate. Archdeacon and Murlin[4] noted a decrease in muscular endurance on the bicycle ergometer in 2 subjects on a diet low in the B complex vitamins (the thiamine intake being 0.27 mg. per day or 0.09 mg. per 1000 calories), the effect being observed within ten to fourteen days on the diet. Addition of the B complex in the form of whole wheat bread or thiamine in pure form resulted in a marked improvement in endurance. Pyridoxine added in 1 experiment had a similar effect but riboflavin had none.

These results are in marked contrast to those of Keys and co-workers. In one experiment[101] already mentioned, no decrease in work performance was noted on diets containing 0.23 mg. thiamine per 1000 calories. In a later paper[104] the Minnesota investigators published the results of a study in which 8 young men were studied before, during, and after a two-week period during which 5 were on a basal diet providing on the average 0.16 mg. of thiamine, 0.15 mg. of riboflavin, and 1.8 mg. of niacin per 1000 calories. These men also received placebos while 3 control subjects were given the same basal diet plus capsules containing a yeast concentrate and synthetic B vitamins. With an energy expenditure of 4800 calories during the experimental period, no differences were noted in endurance and in a variety of clinical, psychologic, and biochemical tests.

In more recent experiments[105] the length of time on a low B complex intake (0.185 mg. thiamine, 0.287 mg. riboflavin, and 3.71 mg. niacin daily per 1000 calories) was extended to 161 days and again no impairment of work performance was noted at a caloric intake and expenditure of 3300 calories. A small increase in blood pyruvate indicated a borderline thiamine deficiency. Immediately thereafter the intake of 2 of the subjects (known as the restricted-deficient group) was restricted much more severely to 0.008 mg. thiamine, 0.013 mg. riboflavin, and 0.1 mg.

niacin daily per 1000 calories with a daily energy intake and expenditure of 4000 calories. Anorexia developed after the first week and by the end of the third week the subjects exhibited almost complete inability to take any food. Supplementation was begun with thiamine alone on the twenty-fourth day. Two additional men who had been on an adequate diet prior to ingesting the very deficient diet (the control-deficient group) exhibited anorexia to a lesser extent. Despite marked changes in general behavior and obvious signs of subjective distress, there were no significant changes in simple strength as measured by grip and back lift. Psychomotor tests of speed and coordination showed slight to marked deterioration. The restricted-deficient subjects showed a rapid and progressive deterioration and incapacity to perform brief severe work. Nausea developed on extreme exertion. Similarly this group was often unable to complete the prescribed daily exercise of moderately hard work, while the control-deficient group was able to perform both types of work. The administration of thiamine alone reversed the deterioration.

Another experiment[8] bearing on this problem involved the maintenance of 7 young men for 35 weeks on a diet that was low in vitamin B complex at a caloric level of approximately 3000. After five weeks, 2 of the subjects received supplements and acted as controls. In the subsequent period the latter showed no decrease in work performance or physical or psychologic appraisal, while the 5 experimental subjects showed definite deterioration in work performance after fifteen weeks on a daily intake of 0.50 mg. thiamine, 0.30 mg. riboflavin, 5.8 mg. niacin, low levels of the other B vitamins, and 45 grams of protein (94 per cent from non-animal sources). When the diet was supplemented with crystalline vitamins, improvement in physical performance tests occurred gradually. No evidence was obtained pointing to an outstanding effect of any one nutrient and improvement was more rapid in subjects receiving the complete group supplementation than in those receiving stepwise additions of nutrients.

One can only conjecture about the reasons for the discrepancy in results obtained in different laboratories. There were obvious differences in the subjects, diets, and experimental conditions. It cannot be over-emphasized that, in the study of the effects of nutritional deficiencies upon functions of the human subject, careful consideration must be given to both psychologic and physiologic factors which may influence the results. Since subjective reactions and individual variability are seriously complicating factors in such experiments, one must exert the greatest caution in accepting the conclusions of experiments not rigidly controlled.

In the only report published on the effects of uncomplicated low riboflavin intake on muscular performance, the Minnesota group[103] found no deleterious effects in 3 men after eighty-four days and, on another 3 men, after one hundred and fifty-two days on a diet containing 0.99 mg. riboflavin per day.

In a study[31] of experimental human ascorbic acid deficiency induced by a diet very low in the vitamin, the first symptom was fatigue which appeared after two months. An impaired capacity for walking and running progressed during the six-month deficiency period. A similar effect of vitamin C deficiency was noted by Farmer[49] in experiments with a group of young men existing for seven months on a diet low in vitamin C.

In view of the ability of the body to store vitamin A so that symptoms may not occur for a year or more on an A-vitamin deficient diet,[167] it is not surprising that no decrease in ability to perform hard muscular exercise was noted in men kept on diets low in vitamin A for about six months.[169]

Do vitamin requirements increase as energy expenditure rises? In this connection Forbes[52] has pointed out three possibilities, namely: "The requirements may be either (a) practically unaltered, or (b) increased in proportion to the work, or (c) increased in proportion to the displacement of the equilibria of the body, that is, show little change until the work becomes really hard and then show a great increase." There is a fourth possibility, namely a relatively large requirement for basal metabolic purposes, with smaller increases associated with increased work. From indirect data on human dietaries associated with the presence or absence of beriberi, and on the basis of animal experiments where the amount of activity or the environmental temperature were varied, or where experimental hyperthyroidism was induced, it has been concluded generally that the requirement for the B complex vitamins, particularly thiamine, is related to total metabolism. In the 1945 Revision of the Recommended Dietary Allowances of the Food and Nutrition Board of the National Research Council[138] it is stated:

> In the original table the thiamine allowances for the several categories were based on the concept that a definite ratio exists between calories and thiamine throughout the entire caloric range. In the conference of consultants in preparation for the 1945 revision it was agreed that the proportion of thiamine required decreases as the calories increase above the lower levels. Despite the change of ratio with calorie level, the custom of relating the thiamine requirement to calories still seems most suitable for practical usage. Acceptance of the concept of decreased proportion of thiamine requirement at the higher caloric levels is responsible for the greatest change made in the thiamine allowances for the present revision . . . it was generally but not unanimously agreed that approximately 0.5 mg. for each 1,000 calories is a reasonable and safe allow-

ance for adults at ordinary low levels of calorie intake. Thus was derived the value of 1.5 mg. for a man receiving 3,000 calories. For very active persons for whom the energy requirement exceeds 3,000 calories the thiamine allowance should be increased 0.3 mg. for each additional 1,000 calories.

In the 1948 revision of the Recommended Dietary Allowances[138a] the practice is retained of recommending increased thiamine intake for increased caloric expenditure but with the explanation "the fact that figures are given for different calorie levels for thiamine and niacin does not imply that we can estimate the requirement of these factors within 500 calories, but they are added merely for simplicity of calculation."

The relation of riboflavin and niacin allowances to caloric intake rests on very scanty evidence. In the 1945 revision the Food and Nutrition Board had adopted the procedure of maintaining approximately the ratio 3:2 between riboflavin and thiamine requirements and 10:1 between niacin and thiamine. However, in the 1948 revision, riboflavin allowances are based on body weight rather than caloric level, so that 1.8 mg. of riboflavin are recommended regardless of energy expenditure for the adult male.

Although work ability is markedly diminished in severe vitamin C deficiency states[31, 49] it is doubtful that hard work brings on scurvy more rapidly. Experiments in which both sedentary and working men were kept on scorbutic diets for eight weeks failed to show any difference between the groups.[90] Fox,[55] in a review of recent European and South African literature on the effect of exercise on vitamin C metabolism and needs, states that the evidence is inconclusive. This same investigator analyzed the histories of over 1000 cases of scurvy occurring in a five-year period among South African native miners and concluded that there was no evidence to suggest that those engaged in strenuous work developed scurvy more often or more quickly than those whose metabolic resources were less severely taxed.[56]

While the evidence is still far from satisfactory on this subject, it appears that no radical elevation in requirements for the vitamins is associated with increased physical activity.

NUTRITION IN ABNORMAL ENVIRONMENTAL CONDITIONS

Influence of Cold Environment on Nutrient Requirements

The energy expended in a cold environment is greater than in temperate or hot environments. The most important of the factors responsible for this are the increased voluntary and involuntary muscular activity resorted to in order to maintain body warmth and the extra work imposed by heavy and cumbersome clothing. There is little increase in basal metabolic rate under conditions of low temperature.

Johnson and Kark[92] found a positive correlation between environmental temperature and caloric intake. American ground troops in Arctic areas ate between 4000 and 5000 calories daily, those in the temperate areas between 3500 and 4200 calories, and those in the tropics between 3100 and 3500 calories; however, the relative composition of the diet voluntarily eaten was much the same for all areas. While more fat was eaten by troops in cold regions, protein and carbohydrate intakes were increased proportionately.

Recent studies with human subjects show that diet and the frequency of feedings may have an effect upon the ability of man to withstand exposure to intense cold.[96, 131] The cooling of the internal tissues of the body was found to be most rapid on a high-protein diet (41 per cent of calories as protein) and least on a high-fat diet (73 per cent of calories), with a high-carbohydrate diet (66 per cent of calories) not quite so effective as a high-fat diet. A high-carbohydrate diet, more than a high-protein diet, definitely lessened the adverse effect of intense cold on the general psychomotor functioning. Fat seemed to be superior to carbohydrate in this respect but differences were obliterated by decreasing the interval between meals to two hours, which, in itself, had a favorable effect on the maintenance of psychomotor functions. The least favorable method of feeding tested was the high-protein diet with one meal (20 per cent of the day's calories) served during an eight-hour exposure, and the most favorable method was the high-fat diet with three 20 per cent meals served during eight hours of exposure. By a change from the first to the second diet plan the decrement in rectal temperature was reduced by two-thirds (1.63°C to 0.57°C) and the decrement in general psychomotor functioning by one-half.[131]

Experiments with animals exposed to cold have been reported by Dugal and colleagues,[40] in which effects of diet on survival and growth were noted. In these respects, a diet rich in fat proved much better for rats kept in a cold room than an equicaloric diet high in carbohydrate.

In observations[41] on the rat, which can synthesize its ascorbic acid, increases were noted in the content of this vitamin in various tissues when the animals had been exposed for some months and had adapted to cold. Rats unable to adapt and dying in the cold had a very low ascorbic acid content. Experiments were then conducted upon guinea pigs, which, like man, require an external source of vitamin C, and it was found that adaptation to cold (as measured by weight gain) depended on the intake of ascorbic acid. An amount of ascorbic acid found adequate at room temperature was reported inadequate at 1° C and below; the lower the temperature, the higher the vitamin C intake required to maintain weight or to allow growth. Adaptation was related to the ascorbic acid level in the tissues, especially in the adrenals. When administration of ascorbic acid was discontinued during exposure to cold, survival was related to the previous level of vitamin C intake. In addition, survival was about twice as long at room temperature as at 0° C. A number of different workers have shown that adrenal cortical extracts increase the resistance to cold in adrenalectomized white rats, and it has been found that the injection of adrenotropic hormone into rats is associated with a rapid and marked drop in the ascorbic acid content of the adrenal gland.[119, 148] Supplementation with a variety of water-soluble vitamins did not appear to have beneficial effect on the tolerance and performance of men in a cold environment.[61]

REQUIREMENTS IN HOT ENVIRONMENTS

The altered nutritional requirements during exposure to heat are quantitative rather than qualitative and involve mainly water and sodium chloride. As the environmental temperature rises in relation to the body temperature, the flow of heat from the body to the environment is impeded. In an attempt to maintain its usual temperature, the body excretes sweat, the evaporation of which removes heat. Water and sodium chloride are the only components of sweat which are apt to be lost in amounts large enough or rapid enough to lead to a condition of deficiency. However, recent work indicates that iron loss, and perhaps that of calcium, may constitute a nutrition problem where sweating is profuse over long periods.[130a] The amounts of other elements lost in this way are not significant.[88, 130a, 159]

The capabilities of the body for sweat loss are great; for example, in one experiment in which young men were subjected to severe stress of temperature and work[46] the maximum sweating rate was 4.2 liters per hour and some men completed four hours of work while sweating at rates of 3 liters per hour, a total amount equal to approximately four times the blood water. While this high rate is not met in industry except in exceptional short-term situations, the loss of a liter of water per hour for an eight-hour day occurs at times in certain heavy industries and, with this volume of water, a total of perhaps 10 to 20 Gm. of salt. Dill *et al.*[38] noted a maximum daily water intake of 11.4 liters among some steel mill workers.

No ill effects occur through such large losses if the water and salt are replaced periodically. However, if proper replacement of salt and water is not made, undesirable consequences occur, ranging from decreased physical and mental performance to death.

A number of investigators have demonstrated that, in a matter of a few hours, physical status and performance of subjects in a hot environment and doing hard work deteriorate (under severe conditions to actual collapse) when water is withheld.[6, 15, 37, 66, 93, 115, 144] Administration of water under these circumstances enables the body to maintain lower rectal and skin temperatures, more normal pulse rates, and more normal physical and mental efficiency. Symptoms of acute water lack during hard work in a hot environment appear to be the most rapidly induced of any deficiency syndrome. Recovery from the effects of dehydration following water ingestion is even more rapid.

Thirst is a reliable guide to water needs under most circumstances. However, men sweating even at moderate rates do not tend to drink water as fast as they evaporate it, although they usually make up the deficiency after the day's work.[2] When the heat load is very high and continued, thirst may fail to insure an adequate intake.[88, 144, 146]

It has been recommended[73, 88] that men working in the heat replace the water lost in sweat by hour-to-hour ingestion of amounts more than sufficient to keep thirst quenched at all times.

The effects of salt deficiency among industrial workers were first pointed out by Moss[133] in connection with "miners' cramps." Since then it has been noted in a variety of occupations among workers exposed to elevated temperatures. The basis of this deficiency is failure to replace adequately the sodium chloride lost in sweat while the water loss is usually made good. Symptoms may include nausea, vomiting, vertigo, mental apathy, exhaustion, painful cramps, and circulatory failure. It is important to note that heat exhaustion due to salt deficiency is not always associated with heat cramps.[112, 160] Workers in hot environments should have ready access to water (preferably cool but not cold) at all times and they should be instructed as to the importance of frequent water and adequate salt intake. Since the average American's daily diet contains 10-15 Gm. of salt and as salt lost in sweat need not be replaced hourly, the salt consumed at mealtimes is adequate for most needs. It is desirable, however, for workers consuming more than 4 quarts of water daily to supplement their dietary salt intake by 1 Gm. of salt for each additional quart of water consumed. This is most satisfactorily supplied in the drinking water in concentrations not higher than 0.2 per cent.[29, 73, 88] The use of salt tablets is less desirable since they frequently cause gastric distress, nausea, and vomiting in some individuals especially during hard work and, more importantly, there is no assurance that those needing salt most will take the tablets. Under circumstances where salted drinking water is not feasible, a recently described[28] slower-dissolving cellulose-impregnated salt tablet may be more desirable than the usual salt-cornstarch tablet.

Both from theoretical considerations and from actual experience, protein foods are as suitable in hot as in cool climates. Recent work on the specific dynamic action of protein in mixed diets has indicated that this is less than it has been considered to be from studies on the specific dynamic action of protein when fed alone.[53, 54] However, even on the basis of the figures for the specific dynamic effect of protein, Johnson[88] has calculated that a meal rich in protein would strain the heat-dissipating mechanisms at the most only 5 per cent as much as moderately hard work (march at a standard Army pace) and concludes that "Although theoretically, at some critical temperature this extra 5 per cent might be a factor limiting work, practically, a high protein diet has little if any deleterious effect upon efficiency for work in the heat." He and his co-workers[143] found that varying the daily protein intake in successive two-month periods from about 100 Gm. to 150 Gm. to 75 Gm. and back to 100 Gm. had no deleterious effect upon ability to march on a treadmill for relatively short periods in humid heat or to perform very hard work of short duration in a temperate environment. These workers challenge the recommendation of Lusk[121] that a high protein diet is contraindicated in hard work especially in hot weather. Certainly, the fact is well-established that acclimatized men in tropical areas who have access to meat eat it and often in large amounts without obvious untoward reactions.

Although there are no well-established figures for optimal intakes of fat or carbohydrate and one cannot speak of actual requirements for these nutrients, it appears that the usual pattern of dietary intake need not be altered in hot climates in order to perform work. It is of interest to note that Forbes *et al.*[53] found that in rats the specific dynamic effect of a mixture of fat and protein is somewhat less than half that anticipated from the values of the individual nutrients and that the addition of fat to carbohydrate or protein or a mixture of the two lowered their dynamic effects. Thus fat in the diet in hot climates should tend to lower heat production.

At least two possibilities exist for changes in vitamin requirements of men at elevated temperature: losses in sweat and altered metabolic requirements.

Losses of vitamins in sweat were studied in a number of laboratories during the recent war.[3, 81, 84-87, 123, 147, 149, 158, 161] The evidence (which has been reviewed briefly by Ershoff[47]) supports the conclusion that, in absolute amounts and in comparison with the urinary excretion of the water-soluble vitamins, losses in sweat are not a significant factor in depleting the body's stores.

There is no evidence that metabolic requirements are increased; the observed increased excretion of pantothenic acid and ascorbic acid may possibly mean a lowered requirement at elevated temperatures. Some popularization of the belief that the need for ascorbic acid is increased has resulted from reports[3, 81] of benefits from large amounts of vitamin C given to workers and from reports[47] that, in hyperpyrexia of infective or artificially induced origin, plasma ascorbic acid levels are reduced. However, Osborne and Farmer[141] were unable to find any reduction in plasma ascorbic acid in patients exposed to a temperature of 102° F in fever cabinets and Abt and co-workers[1] concluded from studies on infectious diseases that hyperpyrexia alone did not affect the vitamin C reserves or utilization. No beneficial effect of large amounts of vitamin C was noted on the ability of young men to work in hot environments for short periods (three hours to four days) nor were there any apparent effects on temperature, vasomotor stability, psychomotor, or strength responses, or on resistance to heat exhaustion.[74]

This subject gained new interest as a result of a series of papers by C. A. Mills and co-workers[124, 125] in which the claim was made that in a hot (91° F) moist environment the requirements for growth of rats for certain vitamins, specifically thiamine and choline, were increased over those at 75° F, while the requirements for riboflavin and other vitamins were not affected. It should be noted, however, that in this work the vitamins were incorporated in the diet so that their intake varied directly with the quantity of the diet ingested. With this procedure, a nutrient present in low amounts in the diet may become a limiting factor, since appetite is depressed at the higher temperature. When thiamine in different amounts was administered to rats *separately* from the ration, it was found that an increase in environmental temperature (78° F to 90° F) resulted in a decreased thiamine requirement.[108] The authors believe that this decrease approximates the decrease in caloric requirement at the elevated temperature. Others[43] also have failed to find increased thiamine requirements at 90° F as compared with 72° F.

Mills has admitted[126] that the absolute thiamine requirement in micrograms per rat per day may be largely unaffected by temperature. However, he makes the point, which is important in itself, that vitamins are usually ingested as part of the diet, and, whenever food intake decreases as a result of high temperatures, a diet adequate in temperate climates may become inadequate with respect to one or more nutrients. In other words, the decrease in the intake of a nutrient at high temperatures may decrease more than the decrease in caloric expenditure. Anorexia and finicky appetites in men exposed to high temperatures are not uncommon and this point is well taken. However, it should not be construed as meaning an increased metabolic or absolute requirement. It does mean that the diets of workers at high temperatures, who find difficulty in eating properly, should be given careful attention.

ANOXIA AND LOW PRESSURE

Although it was suggested in 1908[14] that a carbohydrate diet would be beneficial in alleviating systems of oxygen lack at high altitudes, detailed investigations on human subjects awaited the second World War with its emphasis on aviation. Considerable animal experimentation in a number of laboratories supported and extended the early observations and also indicated that carbohydrate metabolism is affected by exposure to anoxia. Research has elucidated relationships between diet and respiratory quotient (R.Q.) indicating, among other things, that the highest R.Q. occurs after carbohydrate ingestion, that is, there is a minimum demand for oxygen for the yield of carbon dioxide, that frequent ingestion of sugar maintains the high R.Q., that carbohydrate can increase the alveolar oxygen tension and total ventilation, and that maintenance of adequate blood sugar and glycogen reserves are important in the performance of psychomotor functions. Thus, there are good biochemical and physiologic data, as well as actual animal experiments, supporting the belief that diet affects human altitude tolerance.

King and co-workers[106] have carried out studies on the effects of different diets in human subjects maintained at the equivalent of 15,000 to 17,000 feet without oxygen, in whom corticoretinal (peripheral vision) and psychomotor function tests were performed and pulse and respiration rates as well as performance ratings were noted. Significant gains in altitude tolerance over a period of one to four hours could be accomplished by the ingestion of preflight and inflight foods of relatively high carbohydrate content (85 per cent of total calories) in comparison with performance after the omission of a meal, after a single meal high in protein, or after large amounts of fat. Additional experiments[107] in which the length of time at altitude was lengthened to seven hours indicated that a 1000-calorie high-carbohydrate meal (carbohydrate 92 per cent, protein 6 per cent, fat 2 per cent) maintained its advantage over an equicaloric low-carbohydrate meal (carbohydrate 21 per cent, protein 43 per cent, fat 36 per cent) for approximately six hours, but, during the succeeding hour, performances on the two types of meals were nearly equal. The authors emphasize that their findings pertain to immediate preflight and inflight meals which then can be followed by meals correspondingly high in protein, so that there is no departure from normal requirements or accepted dietary practices relative to food intake as a whole. Other studies employing human subjects have generally supported these findings.[42, 65]

There is no evidence that mild vitamin deficiency states have any effect on human altitude tolerance.[58]

Nutrition and Resistance to Toxic Compounds

It must be emphasized that, though nutritional factors may influence resistance to toxic compounds, the principal control of such hazards in industry lies in engineering applications which protect the workers from exposure to potentially harmful concentrations of toxic substances. However, it is sometimes difficult or impossible to afford complete protection by engineering methods. In any event, it is desirable to develop all practical means of protecting the health of persons whose work necessitates contact with potentially harmful substances. Nutrition offers possibilities which warrant more study.[127, 151, 152]

CHLORINATED HYDROCARBONS

More than thirty years ago it was noted that animals fed a high-carbohydrate diet were less susceptible to chloroform anesthesia than those on a diet rich in fat.[63, 139] It was also found that liver regeneration following chloroform poisoning occurred more rapidly in animals on a high-carbohydrate diet than in those on a high-fat diet. A high-protein intake exerted a protective effect while starvation increased susceptibility.[35] Carbon tetrachloride toxicity was also demonstrated to be ameliorated by diet.[34]

Miller and Whipple[128] found the extent of liver injury in dogs treated with chloroform to increase as the body stores of protein were depleted, while methionine or cystine plus choline, administered before or up to four hours after the chloroform, gave significant protection.[129] Methionine given at the onset of chloroform anesthesia to dogs on a stock diet supposedly adequate also conferred protection.[16] The survival time of rats exposed to methyl chloride was extended when the casein content of the diet was increased above a low level of 9 per cent. The sulphur-containing amino acids, methionine and cystine, supplemented the protective action of increased protein.[155] Ethylene dichloride and propylene dichloride, used industrially as solvents, were more toxic to rats on a low-protein diet than on an adequate protein intake, while methionine or cystine plus choline, supplementary to the low-protein intake, greatly increased resistance.[75, 77, 78]

Bollman found carbohydrate to be more protective than protein against carbon tetrachloride.[9] György *et al.*[67] observed a protective action of supplementary protein and methionine fed to rats subsisting on a diet low in protein, and stated that the beneficial influence of the supplements seemed to be more on the kidney than on the liver.

There have been several reports[7, 45] on the favorable effects of methionine together with casein digest or intravenous glucose and high-protein diet in the treatment of human CCl_4 poisoning. This work is certainly not conclusive and in a recent article the Council on Pharmacy and Chemistry of the American Medical Association urged further clinical trial.[30] Another reason for caution in translating results from animals to man is the evidence that the human requirements for methionine differ quantitatively and perhaps qualitatively from those of the dog and rat.[44]

AROMATIC NITRO COMPOUNDS

During the First World War the toxicity of trinitrotoluene (TNT) presented an industrial health problem of major importance and it was postulated by some that diet might play a role in worker-susceptibility to poisoning by that substance. Since then a number of recommendations have been made for dietary measures as prophylaxis or therapy in the munitions industries; these have included high-carbohydrate diets, large amounts of vitamin C, calcium, milk, or a combination of nutrients.

A field study carried out among the workers in a TNT bomb and shell loading plant in the U. S. in 1945 by Sievers *et al.*[153] failed to demonstrate any significant effect of milk or of polyvitamin preparations on the incidence and severity of TNT intoxication; however, the number of employees evidencing any signs of TNT poisoning was too small to permit definitive conclusions.

Animal experiments have shown that the composition of the diet influences susceptibility to aromatic nitrobenzene compounds.[26, 27, 79, 156, 168] Himsworth and Glynn[79] demonstrated with rats that severe symptoms and marked pathological lesions resembling those seen in severe human poisoning developed in the animals receiving a high-fat diet which was also rather low in protein. Those rats partaking of a high-carbohydrate, low-fat, barely adequate protein diet exhibited only slight ill effects from the TNT while those on a high-protein, low-fat diet appeared normal. Others[156] have found increased susceptibility of rats on a low-protein diet. Working with the related compound, 2, 4-dinitrotoluene, Clayton and Baumann[26, 27] found that mice were more resistant when on a high-fat diet than on a low-fat diet. Shils and Goldwater[152a] have confirmed the beneficial effect of fat on the resistance of rats to 2, 4-dinitrotoluene, but, unlike Himsworth and Glynn,[79] found high fat diets only slightly more deleterious than low-fat diets when TNT was administered.

It has been found that ascorbic acid had little effect on the course of chronic TNT poisoning in normal rats,[156] guinea pigs,[156] rabbits,[156] and dogs.[39] Cats, which are relatively highly susceptible to TNT, appeared to be benefited to some extent by this vitamin.[156] While guinea pigs did not benefit by large amounts of ascorbic acid, their resistance to TNT was lowered in the vitamin C deficiency state.[113]

Reference has been made to observations on the possible beneficial influence of milk on human TNT poisoning, and it is of some interest to note the results of experiments on the effect of milk given to dogs which were treated with TNT.[39] There was no evidence that milk promoted detoxication, since the blood changes were similar to those in control animals not receiving milk. However, the animals receiving milk lost less weight and the inflammatory reactions in the intestinal tract were as a rule less severe. In the milk-fed dogs the intestinal mucosa was covered with a fibromucoid film not seen in the control animals, indicating that milk may have had a demulcent action which protected the mucous membrane and interfered with TNT absorption.

BENZENE (BENZOL)

Benzene toxicity has been found to be greater in animals maintained on a low-protein than on high-protein intake; the effect of variations in fat intake does not appear to be nearly as marked as that of variations in protein intake.[116-118]

A considerable number of papers have appeared in the German, French, and Italian literature claiming that ascorbic acid is beneficial in experimental and industrial benzene poisoning.[152] However, both the animal and human observations must be considered inconclusive because of inadequate control precautions or insufficient numbers of subjects.

Individual reports have been made of unsuccessful attempts to influence the leukopenia of benzene poisoning with a folic-acid-containing liver extract given to rats[145] and with pyridoxine in human subjects.[109]

LEAD

Lead enters the body most commonly through the gastrointestinal and respiratory tracts, with the ingested lead compounds dissolving to some extent in the gastric and intestinal juices. It has been proposed[20] that foods be eaten which depress or retard gastric secretion during lead exposure, and milk was suggested for this purpose. The inhibition of lead absorption by milk has been reported and attributed to the possible formation of an insoluble lead phosphate.[132] However, Aub and coworkers[5] as well as Kehoe *et al.*[97] were unable to find any significant influence of milk upon lead absorption from the gastrointestinal tract.

Recently it has been reported that iron salts such as iron citrate reduced the toxicity of lead.[76] There is a difference of opinion as to the clinical value of the dietary treatment of lead poisoning.[5, 19, 95]

There seems little doubt that the calcium and phosphorus levels of the diet influence absorption and bone deposition of lead in experimental animals. A number of investigators[18, 64, 114, 150, 157, 163] have found that high calcium diets fed to animals depressed lead retention, while a low calcium intake increased lead retention. It is of interest to note that in rat experiments where moderate amounts of lead were fed, Shields and Mitchell[150] found that the only method of securing lead storage was to lower the calcium content of the diet to inadequate or borderline levels. Kehoe and colleagues[98] gave 2 healthy human subjects 1 and 2 mg. of soluble lead daily for forty and twenty-three months respectively. Variations in calcium and phosphorus intake had no appreciable influence on the absorption and gross retention of the lead.

Vitamin C has been reported to be beneficial in human lead poisoning;[82, 122] however, Evans and co-workers[48] were unable to find any significant effect of 100 mg. daily doses of ascorbic acid given to workers in a plant making tetraethyl lead. Other investigators[32, 142] also have found no beneficial effect of this vitamin in connection with lead poisoning.

This brief review indicates chiefly negative findings in the work on man. However, it must be emphasized that we are still in the early stage of observation and classification, without much understanding of the underlying causes for the positive dietary effects on toxicity which have been observed. The information available from the results of studies of nutrition and its relation to resistance to toxic substances in animals does indicate that it would be a conservative preventive procedure for men and women who work under conditions of exposure to substances known to produce damage to the liver or to the hemopoietic system to consume habitually diets relatively high in good quality protein, adequate in calories, and perhaps modest in fat content. Further, it would seem desirable that all persons exposed to noxious substances of any kind in industry be maintained in the best possible nutritional status in regard to all nutrients.

BIBLIOGRAPHY

1. Abt, A. F., Hardy, L. M., Farmer, C. J., and Maaske, J. D. Relation of vitamin C to scarlet fever, rheumatic infections and diphtheria in children. *Am. J. Dis. Child.* 64:426, 1942.
2. Adolph, E. F., and Dill, D. B. Observations on water metabolism in the desert. *Am. J. Physiol.* 123:369, 1938.

3. Anonymous Vitamin C prevents heat cramps and heat prostration. *Science* (Suppl.) 95:12, 1942.
4. Archdeacon, J. W., and Murlin, J. R. The effect of thiamine depletion and restoration on muscular efficiency and endurance. *J. Nutrition* 28:241, 1944.
5. Aub, J. C., Fairhall, L. T., Minot, A. S., and Reznikoff, P. Lead Poisoning. Baltimore, Williams and Wilkins, 1926.
6. Bean, W. B., and Eichna, L. W. Performance in relation to environmental temperature. *Federation Proc.* 2:144, 1943.
7. Beattie, J., Herbert, P. H., Wechtel, C., and Steele, C. W. Studies on hepatic dysfunction: I., Carbon tetrachloride poisoning treated with casein digest and methionine. *Brit. M. J.* 1:209, 1944; II., Carbon tetrachloride poisoning; sulfur metabolism. *Brit. M. J.* 2:847, 1944.
8. Berryman, G. H., Henderson, C. R., Wheeler, W. C., Cogswell, R. C., Jr., Spinells, J. R., Grundy, W. S., Johnson, H. C., Wood, M. E., Denko, C. W., Friedemann, T. E., Harris, S. C., Ivy, A. C., and Youmans, J. B. Effects in young men consuming restricted quantities of B complex vitamins and protein, and changes associated with supplementation. *Am. J. Physiol.* 148:165, 1944.
9. Bollman, J. L. Protective value of foods in experimental cirrhosis. *Ann. Int. Med.*, 12:1, 1938; *J.A.M.A.* 121:1413, 1943.
10. Borsook, H. Nutritional status of aircraft workers in southern California: III., Effects of vitamin supplementation on absenteeism, turnover and personnel ratings. *Milbank Mem. Fund Quart.* 23:113, 1945.
11. Borsook, H., Alpert, E., and Keighley, G. L. Nutritional status of aircraft workers in southern California: II., Clinical and laboratory findings. *Milbank Mem. Fund Quart.* 23:113, 1945.
12. Borsook, H., Dubnoff, J. W., Keighley, G., and Wiehl, D. G. Nutritional status of aircraft workers in southern California: IV., Effects of vitamin supplementation on clinical, instrumental, and laboratory findings and symptoms. *Milbank Mem. Fund Quart.* 24:99, 1946.
13. Borsook, H., and Wiehl, D. G. Nutritional status of aircraft workers in southern California: V., A conspectus of the survey and its field. *Milbank Mem. Fund Quart.* 24:251, 1946.
14. Boycott, A. E., and Haldane, J. S. The effects of low atmospheric pressures on respiration. *Am. J. Physiol.* 37:355, 1908.
15. Brown, A. H. Dehydration exhaustion, Chapter 13 in Adolph, E. F., *et al.* Physiology of Man in the Desert. New York, Interscience, 1947.
16. Brunschwig, A., Nichols, S., Bigelow, R. R., and Miles, O. J. Sulfhydryl protection of the liver. *Arch. Path.* 40:81, 1945.
17. Burnet, E., and Aykroyd, W. R. Nutrition and public health. *Quart. Bull. Health Organ., League of Nations* 4:323, 1935.
18. Calvery, H. O., Laug, E. P., and Morris, H. J. The chronic effects on dogs of feeding diets containing lead acetate, lead arsenate, and arsenic trioxide in varying concentrations. *J. Pharmacol. & Exper. Therap.* 64:364, 1938.

19. Cantarow, A., and Trumper, M. Lead poisoning. Baltimore, Williams and Wilkins, 1944.

20. Carlson, A. J., and Woelfel, A. The solubility of white lead in human gastric juice and its bearing on the hygiene of the lead industries. *Am. J. Pub. Health* 3:755, 1913.

21. Cathcart, E. P., and Burnett, W. A. The influence of muscle work on metabolism in varying conditions of diet. *Proc. Roy. Soc.*, London, *s. B* 99:405, 1926.

22. Chittenden, R. H. Physiological Economy in Nutrition. New York, Stokes, 1904.

23. Christensen, E. H., and Hansen, O. Arbeitsfähigkeit und Ernährung. *Skandinav. Arch. f. Physiol.* 81:160, 1939.

24. Christensen, E. H., Krogh, A., and Linhard, J. Investigations on heavy muscular work. *Quart. Bull. Health Organ., League of Nations* 3:388, 1934.

25. Clarke, D., DeJongh, T. W., and Jokl, E. Effect of mid-day meal upon physical efficiency of school children. *Manpower* 1:30, 1943.

26. Clayton, C. C., and Baumann, C. A. Some effects of diet on the resistance of mice toward 2, 4-dinitrotoluene. *Arch. Biochem.* 5:115, 1944.

27. Clayton, C. C., and Baumann, C. A. Effect of fat and calories on the resistance to 2, 4-dinitrotoluene. *Arch. Biochem.* 16:415, 1948.

28. Consolazio, W. V., Pecora, L. J., and Tusing, T. A slow dissolving non-irritating salt tablet for use in hot environments. *J. Indust. Hyg. & Toxicol.* 29:347, 1947.

29. Council on Pharmacy and Chemistry, A.M.A. The addition of salt to drinking water. *J.A.M.A.* 129:131, 1945.

30. Council on Pharmacy and Chemistry. The status of methionine in the prevention and treatment of liver injury. *J.A.M.A.* 133:107, 1947.

31. Crandon, J. H., Lund, C. C., and Dill, D. B. Experimental human scurvy. *New England Med. J.* 223:353, 1940.

32. Dannenberg, A. M., Widerman, A. H., and Friedman, P. S. Ascorbic acid in treatment of chronic lead poisoning: Report of case of Clinical failure. *J.A.M.A.* 114:1439, 1940.

33. Darling, R. C., Johnson, R. E., Pitts, G. C., Consolazio, F., and Robinson, P. F. Effects of variations in dietary protein on the physical well-being of men doing manual work. *J. Nutrition* 28:273, 1944.

34. Davis, N. C. The influence of diet upon the liver injury produced by carbon tetrachloride. *J. M. Research* 44:601, 1924.

35. Davis, N. C., and Whipple, G. H. The influence of fasting and various diets on the liver injury effected by chloroform anaesthesia. *Arch. Int. Med.* 23:612, 1919.

36. Dill, D. B. The economy of muscular exercise. *Physiol. Rev.* 16:263, 1936.

37. Dill, D. B. Life, Heat and Altitude. Cambridge, Harvard, 1939.

38. Dill, D. B., Bock, A. V., Edwards, H. T., and Kennedy, P. H. Industrial fatigue. *J. Indust. Hyg. & Toxicol.* 18:417, 1936.

39. Donahue, D. D., Monaco, A. R., and Von Oettingen, W. F. Experimental studies on the toxicity and potential dangers of trinitrotoluene (TNT): XII., Relationship between dietary factors and TNT poisoning in dogs. *Pub. Health Bull.* 285:56, 1944.

40. Dugal, L. P., Leblond, C. P., and Thérien, M. Resistance to extreme temperatures in connection with different diets. *Canad. J. Research* 23:244, 1945.

41. Dugal, L. P., and Thérien, M. Ascorbic acid and acclimatization to cold environment. *Canad. J. Research* 25:111, 1947.

42. Eckman, M., Barach, B., Fox, C. A., Rumsey, C. C., Jr., and Barach, A. L. Effect of diet on altitude tolerance. *J. Aviation Med.* 16:328, 1945.

43. Edison, A. O., Silber, R. H., and Tennent, D. M. The effect of varied thiamine intake on the growth of rats in tropical environment. *Am. J. Physiol.* 144:643, 1945.

44. Editorial Methionine in human nutrition. *J.A.M.A.* 134:956, 1947.

45. Eddy, H. J. Jr. Carbon tetrachloride poisoning: A preliminary report on the use of methionine in hepatitis. *J.A.M.A.* 128:994, 1945.

46. Eichna, L. W., Ashe, W. F., Bean, W. B., and Shelley, W. B. The upper limits of environmental heat and humidity tolerated by acclimatized men working in hot environments. *J. Indust. Hyg. & Toxicol.* 27:59, 1945.

47. Ershoff, B. H. Conditioning factors in nutritional disease. *Physiol. Rev.* 28:107, 1948.

48. Evans, E. E., Norwood, W. D., Kehoe, R. A., and Machle, W. Effects of ascorbic acid in relation to lead absorption. *J.A.M.A.* 121:501, 1943.

49. Farmer, C. J. Some aspects of vitamin C metabolism. *Federation Proc.* 3:179, 1945.

50. Foltz, E. E., Barborka, C. J., and Ivy, A. C. The level of vitamin B-complex in the diet at which detectable symptoms of deficiency occur in man. *Gastroenterology* 2:323, 1944.

51. Foltz, E. E., Ivy, A. C., and Barborka, C. J. Influence of components of the vitamin B complex on recovery from fatigue. *J. Lab. & Clin. Med.* 27:1396, 1942.

52. Forbes, W. H. The effects of hard physical work upon nutritional requirements. *Milbank Mem. Fund Quart.* 23:89, 1945.

53. Forbes, E. B., and Swift, R. W. Associative dynamic effects of protein, carbohydrate and fat. *J. Nutrition* 27:453, 1944.

54. Forbes, E. B., Swift, R. W., Marcy, L. F., and Davenport, M. T. Protein intake and heat production. *J. Nutrition* 28:189, 1944.

55. Fox, F. W. Ascorbic acid (vitamin C) and human nutrition: A critical review of the more recent literature. *Proc. Transvaal Mine Medical Off. Assoc.* 19:1, 1940.

56. Fox, F. W. Scurvy on the Witwatersrand gold mines: A consideration of some statistical data. *Proc. Transvaal Mine Medical Off. Assoc.* 19:53, 1940.

57. Frankau, I. M. Acceleration of coordinated muscular effort by nicotinamide: Preliminary report to the Medical Research Council. *Brit. M. J.* 2:601, 1943.

58. Friedemann, T. E., and Ivy, A. C. Work at high altitude: I., Plan of study and methods. *Quart. Bull. Northwestern Univ. Med. School* 21:31, 1947; Harris, S. C., Ivy, A. C., and Friedemann, T. E. II., The effect of training and dietary restriction of thiamine and riboflavin on altitude tolerance and physical efficiency for work at a simulated altitude of 15,000 feet. *Quart. Bull. Northwestern Univ. Med. School* 21:135, 1947.

59. Garry, R. C. The static effort and the excretion of uric acid. *J. Physiol.* 62:364, 1927.

60. Gemmill, C. L. The fuel for muscular exercise. *Physiol. Rev.* 22:32, 1942.

61. Glickman, N., Keeton, R. H., Mitchell, H. H., and Fahnestock, M. K. The tolerance of man to cold as affected by dietary modifications: High *versus* low intake of certain water soluble vitamins. *Am. J. Physiol.* 146:538, 1946.

62. Goodhart, R. S. Nutrition in Industry. Montreal, International Labor Office, 1946.

63. Graham, E. A. The resistance of pups to late chloroform poisoning in its relation to liver glycogen. *J. Exper. Med.* 21:185, 1915.

64. Grant, R. L., Calvery, H. O., Laug, E. P., and Morris, H. J. The influence of calcium and phosphorus on the storage and toxicity of lead and arsenic. *J. Pharmacol. & Exper. Therap.* 64:446, 1938.

65. Green, D. M., Butts, J. S., Mulholland, H. F. The relationship of anoxia susceptibility to diet. *J. Aviation Med.* 16:311, 1945.

66. Gregory, R. A., and Lee, D. H. K. Effect of water intake upon human reactions to reduced cooling powers. *J. Physiol.* 86:204, 1936.

67. György, P., Seifter, J., Tomarelli, R. M., and Goldblatt, H. Influence of dietary factors and sex on toxicity of carbon tetrachloride in rats. *J. Exper. Med.* 83:449, 1946.

68. Haggard, H. W., and Greenberg, L. A. Diet and Physical Efficiency. New Haven, Yale, 1935.

69. Haggard, H. W., and Greenberg, L. A. Between-meal feeding in industry: Effects on absenteeism and attitude of clerical employees. *J. Am. Dietet. A.* 15:435, 1939.

70. Haldi, J., Bachmann, G., Ensor, C., and Wynn, W. Muscular efficiency in relation to the taking of food and to the height of the respiratory quotient immediately before exercise. *Am. J. Physiol.* 121:123, 1938.

71. Haldi, J., and Wynn, W. The effect of low and high carbohydrate meals on the blood sugar level and on work performance in strenuous exercise of short duration. *Am. J. Physiol.* 145:402, 1945–46.

72. Haldi, J., and Wynn, W. Work performance, respiratory exchange, and certain blood constituents after isocaloric meals of low and high carbohydrate content. *J. Nutrition* 33:287, 1947.

73. Hastings, A. B., and Guest, G. Summary of report on salt and water requirements. *Bull. Food and Nutrition Board, National Research Council* 4:167, 1944.

74. Henschel, A., Taylor, H. L., Brozek, J., Mickelsen, O., and Keys, A. Vitamin C and ability to work in hot environments. *Am. J. Trop. Med.* 24:259, 1944.

75. Heppel, L. A., Highman, B., and Porterfield, V. T. Toxicology of 1, 2-dichloropropane (propylene dichloride): II., Influence of dietary factors on the toxicity of dichloropropane. *J. Pharmacol. & Exper. Therap.* 87:11, 1946.

76. Heppel, L. A., and Kornberg, A. Influence of iron salts on the toxicity of lead. *Proc. Soc. Exper. Biol. & Med.* 61:220, 1946.

77. Heppel, L. A., Neal, P. A., Daft, F. S., Endicott, K. M., Orr, M. L., and Porterfield, V. T. Toxicology of 1, 2-dichloroethane (ethylene dichloride): I., Influence of dietary factors on toxicity of dichlorethane. *J. Indust. Hyg. & Toxicol.* 27:15, 1945.

78. Heppel, L. A., Neal, P. A., Perrin, T. L., Endicott, K. M., and Porterfield, V. T. The toxicology of 1, 2-dichlorethane (ethylene dichloride): III., Its acute toxicity and the effect of protective agents. *J. Pharmacol. & Exper. Therap.* 84:53, 1945.

79. Himsworth, H. P. and Glynn, L. E. Experimental trinitrotoluene poisoning; the effect of diet. *Clin. Sc.* 4:421, 1942.

80. Holmes, A. D., Pigott, M. G., Sawyer, W. A., and Comstock, L. Results of supplementing the dietary of substandard workers with cod liver oil and milk. *J. Indust. Hyg. & Toxicol.* 14:207, 1932.

81. Holmes, H. N. Vitamin C in the war. *Science* 96:384, 1942.

82. Holmes, H. N., Campbell, K., and Amberg, E. J. Effect of vitamin C on lead poisoning. *J. Lab. and Clin. Med.*, 24:1119, 1939.

83. Ivy, A. C. The physiology of work. *J.A.M.A.* 118:569, 1942.

84. Johnson, B. C., Hamilton, T. S., and Mitchell, H. H. The effect of choline intake and environmental temperature on the excretion of choline from the human body. *J. Biol. Chem.* 159:5, 1945.

85. Johnson, B. C., Hamilton, T. S., and Mitchell, H. H. The excretion of nicotinic acid, nicotinamide, nicotinuric acid, and N^1-methylnicotinamide by normal individuals. *J. Biol. Chem.* 159:231, 1945.

86. Johnson, B. C., Mitchell, H. H., and Hamilton, T. S. Occurrence of inositol and of p-aminobenzoic acid in sweat. *J. Biol. Chem.* 161:357, 1945.

87. Johnson, B. C., Hamilton, T. S., and Mitchell, H. H. The excretion of pyridoxine, "pseudopyridoxine," and 4-pyridoxic acid in the urine and sweat of normal individuals. *J. Biol. Chem.* 158:619, 1945.
88. Johnson, R. E. Nutritional standards for men in tropical climates. *Gastroenterology* 1:832, 1943.
89. Johnson, R. E., Darling, R. C., Forbes, W. H., Brouha, L., Egana, E., and Graybiel, A. The effects of a diet deficient in part of the vitamin B complex upon men doing manual labor. *J. Nutrition* 24:585, 1942.
90. Johnson, R. E., Darling, R. C., Sargent, F., and Robinson, P. Effects of variations in dietary vitamin C on the physical well-being of manual workers. *J. Nutrition* 29:155, 1945.
91. Johnson, R. E., and Kark, R. M. Feeding problems in man as related to environment. Chicago, Illinois. Research Report of the Quartermaster Food and Container Institute for the Armed Forces, 1947.
92. Johnson, R. E., and Kark, R. M. Environment and food intake in man. *Science* 106:378, 1947.
93. Johnson, R. E., Pitts, G. C., and Consolazio, F. C. Factors influencing chloride concentration in human sweat. *Am. J. Physiol.* 141:575, 1944.
94. Johnstone, R. T. Occupational Diseases. Philadelphia, Saunders, 1942.
95. Jokl, E., and Suzmann, M. A study of the effects of vitamin C upon physical efficiency, Appendix II to Fox, F. W., and Dangerfield, L. F. Scurvy and the requirements of native mine labourers for the anti-scorbutic vitamin: An experimental study. *Proc. Transvaal Mine Medical Off. Assoc.* 19:19, 1939.
96. Keeton, R. W., Lambert, E. H., Glickman, N., Mitchell, H. H., Last, J. H. and Fahnestock, M. K. The tolerance of man to cold as affected by dietary modifications: Proteins *versus* carbohydrates, and the effect of variable protective clothing. *Am. J. Physiol.* 146:66, 1946.
97. Kehoe, R. A., Cholak, J., Hubbard, D. M., Bamback, K., and McNary, R. C. Experimental studies on lead absorption and excretion and their relation to the diagnosis and treatment of lead poisoning. *J. Indust. Hyg. & Toxicol.* 25:71, 1943.
98. Keys, A. Physical performance in relation to diet. *Federation Proc.* 2:164, 1943.
99. Keys, A. Human starvation and its consequences. *J. Am. Dietet. A.* 22:582, 1946. Experimental human starvation—general and metabolic results of a loss of one-fourth the body weight in six months. *Federation Proc.* 5:55, 1946.
100. Keys, A. Caloric undernutrition and starvation, with notes on protein deficiency. *J.A.M.A.* 138:500, 1948.
101. Keys, A., and Henschel, A. F. Vitamin supplementation of U. S. Army rations in relation to fatigue and the ability to do muscular work. *J. Nutrition* 23:259, 1942.
102. Keys, A., Henschel, A. F., Mickelsen, O., and Brozek, J. M. The performance of normal young men on controlled thiamine intakes. *J. Nutrition* 26:399, 1943.

103. Keys, A., Henschel, A. F., Mickelsen, O., Brozek, J., and Crawford, J. H. Physiological and biochemical functions in normal young men on a diet restricted in riboflavin. *J. Nutrition* 27:165, 1944.

104. Keys, A., Henschel, A., Taylor, H. L., Mickelsen, O., and Brozek, J. Absence of rapid deterioration in men doing hard physical work on a restricted intake of vitamins of the B complex. *J. Nutrition* 27:485, 1944.

105. Keys, A., Henschel, A., Taylor, H. L., Mickelsen, O., and Brozek, J. Experimental studies on man with a restricted intake of B vitamins. *Am. J. Physiol.* 144:5, 1945.

106. King, C. G., Bickerman, H. A., Bouvet, W., Harrer, C. J., Oyler, J. R., and Seitz, O. P. Aviation nutrition studies: I., Effects of pre-flight and in-flight meals of varying composition with respect to carbohydrate, protein and fat. *J. Aviation Med.* 16:69, 1945.

107. King, C. G., Bouvet, W., Crook, M. N., Harrer, C. J., Oyler, J. R., and Schwimmer, D. Observations on the effect of pre-flight meals upon altitude tolerance. *Science* 102:36, 1945.

108. Kline, O. L., Friedman, L., and Nelson, E. M. The effect of environmental temperature on thiamine requirement of the rat. *J. Nutrition* 21:35, 1945.

109. Knutson, D., Oldfelt, C. O., and Wising, P. The treatment of leukopenia and granulocytopenia with pyridoxine (vitamin B_6). *Acta med. Scandinav.* 125:326, 1946.

110. Kraut, H. A., and Muller, A. E. Calorie intake and industrial output. *Science* 104:495, 1946.

111. Krogh, A., and Linhard, J. The relative value of fat and carbohydrate as sources of muscular energy. *Biochem. J.* 14:290, 1920.

112. Ladell, W. S. S., Waterlow, J. C., and Hudson, M. F. Desert climate: Physiological and clinical observations. *Lancet* 2:491, 1944.

113. Lawton, A. H., Monaco, A. R., and Von Oettingen, W. F. Experimental studies on the toxicity and potential dangers of trinitrotoluene (TNT): XIII., Effects of feeding ascorbic acid on TNT poisoning in Guinea pigs. *Pub. Health Bull.* 285:66, 1944.

114. Lederer, L. G., and Bing, F. C. Effect of calcium and phosphorus on the retention of lead by the growing organism. *J.A.M.A.* 114:2457, 1940.

115. Lee, D. H. K., and Boissard, G. P. B. The effect of exercise in hot atmospheres upon the pulse rate. *M. J. Australia* D:664, 1940.

116. Li, T. W., and Freeman, S. The effect of protein and fat content of the diet upon the toxicity of benzene for rats. *Am. J. Physiol.* 145:158, 1945.

117. Li, T. W., and Freeman, S. The effect of methionine on protein-deficient rats exposed to benzene. *Am. J. Physiol.* 148:358, 1947.

118. Li, T. W., Freeman, S., Hough, V. H., and Gunn, F. D. The increased susceptibility of protein-deficient dogs to benzene poisoning. *Am. J. Physiol.* 145:166, 1945.

119. Long, C. N. H. Recent studies on the function of the adrenal cortex. *Bull. New York Acad. Med.* 23:260, 1947.

120. Lundbaeck, K. Fasting values of blood sugar, RQ, and alveolar CO_2 tension on high and low carbohydrate diets. *Acta Physiol. Scandinav.* 7:29, 1944.

121. Lusk, G. The Science of Nutrition, (ed. 4). Philadelphia, Saunders, 1931.

122. Marchmont-Robinson, S. W. Effect of Vitamin C on Workers Exposed to Lead Dust. *J. Lab. & Clin. Med.* 26:1478, 1941.

123. Mickelsen, O., and Keys, A. The composition of sweat, with special reference to the vitamins. *J. Biol. Chem.* 149:479, 1943.

124. Mills, C. A. Environmental temperatures and thiamine requirements. *Am. J. Physiol.* 133:525, 1941.

125. Mills, C. A. Environmental temperatures and B-vitamin requirements. *Arch. Biochem.* 1:73, 1942.

126. Mills, C. A. Letter to the Editor. *Nutrition Rev.* 2:127, 1944.

127. Miller, L. L. Nutritional factors affecting the toxicity of halogenated hydrocarbons. *Occup. Med.* 5:194, 1948.

128. Miller, L. L., and Whipple, G. H. Chloroform liver injury increase as protein stores decrease. *Am. J. M. Sc.* 199:204, 1940.

129. Miller, L. L., and Whipple, G. H. Liver injury, liver protection and sulfur metabolism: Methionine protects against chloroform liver injury even when given after anesthesia. *J. Exper. Med.* 76:421, 1942.

130. Mitchell, H. H. Adaptation to undernutrition. *J. Am. Dietet. A.* 20:511, 1944.

130a. Mitchell, H. H., and Hamilton, T. S. The dermal excretion under controlled environmental conditions of nitrogen and minerals in human subjects, with particular reference to calcium and iron. *J. Biol. Chem.* 178:345, 1949.

131. Mitchell, H. A., Glickman, N., Lambert, E. H., Keeton, R. W., and Fahnestock, M. K. The tolerance of man to cold as affected by dietary modification: Carbohydrate *versus* fat and the effects of the frequency of meals. *Am. J. Physiol.* 146:84, 1946.

132. Miyasaki, S. Zur Pharmakologie des Bleies. V. Die Resorption des Metalls von Magen-Darmkanal und die Moglichkeit ihrer Beeinflussung. *Arch. f. exper. Path. u. Pharmakol* 160:39, 1930.

133. Moss, K. N. Some effects of high air temperatures and muscular exertion upon colliers. *Proc. Roy. Soc. London, s. B.* 95:181, 1923–24.

34. National Research Council Inadequate Diets and Nutritional Deficiencies in the United States. Washington, D. C., Bulletin No. 109, 1943.

135. National Research Council Recommended Dietary Allowances. Washington, D. C., Reprint & Circular Series No. 115, 1943.

136. National Research Council. *Proceedings of the Food and Nutrition Board* 4:30, 1944.

137. National Research Council The Nutrition of Industrial Workers (Second Report of the Committee on the Nutrition of Industrial Workers). Washington, D. C., Reprint and Circular Series No. 123, 1945.

138. National Research Council Recommended Dietary Allowances, Revised 1945. Washington, D. C., Reprint & Circular Series No. 122, 1945.

138a. National Research Council Recommended Dietary Allowances, Revised 1948. Washington, D. C., Reprint and Circular Series No. 129, 1948.

139. Opie, E. L., and Alford, L. B. The influence of diet upon necrosis caused by hepatic and renal poisons: I., Diet and the hepatic lesions of chloroform, phosphorus or alcohol. *J. Exper. Med.* 21:1, 1915.

140. Orr, J. B., and Leitch, I. The determination of the calorie requirements of man. *Nutrition Abstr. & Rev.* 7:509, 1938.

141. Osborne, S. L., and Farmer, C. J. Influence of hyperpyrexia on ascorbic acid concentration in the blood. *Proc. Soc. Exper. Biol. & Med.* 49:575, 1942.

142. Pillemer, L., Seifter, J., Kuehn, A. O., and Ecker, E. E. Vitamin C in chronic lead poisoning: An experimental study. *Am. J. Med. Sc.* 200:322, 1940.

143. Pitts, G. C., Consolazio, F. C., and Johnson, R. E. Dietary protein and physical fitness in temperate and hot environments. *J. Nutrition* 27:497, 1944.

144. Pitts, G. C., Johnson, R. E., and Consolazio, F. C. Work in the heat as affected by intake of water, salt, and glucose. *Am. J. Physiol.* 142:253, 1944.

145. Platt, W. R., Bluestein, S. G., and Sisson, R. G. The effect of liver extract and methyl acetamide with parachloro-xylenol on artificially induced leukopenia in rats. *Yale J. Biol. & Med.* 18:275, 1946.

146. Rothstein, A., Adolph, E. F., and Wills, J. H. Voluntary dehydration. Chapter 16 in Adolph, E. F., *et al.* Physiology of Man in the Desert. New York, Interscience, 1947.

147. Sargent, F., Robinson, P., and Johnson, R. E. Water-soluble vitamins in sweat. *J. Biol. Chem.* 153:285, 1944.

148. Sayers, G., Sayers, M. A., Lewis, H. L., and Long, C. N. H. Effect of adrenotropic hormone on ascorbic acid and cholesterol content of the adrenal. *Proc. Soc. Exper. Biol. & Med.* 55:238, 1944.

149. Shields, J. B., Johnson, B. C., Hamilton, T. S., and Mitchell, H. H. Excretion of ascorbic acid and dehydroascorbic acid in sweat and urine under different environmental conditions. *J. Biol. Chem.* 161:351, 1945.

150. Shields, J. B., and Mitchell, H. H. Effect of calcium and phosphorus on the metabolism of lead. *J. Nutrition* 21:541, 1941.

151. Shils, M. E. Applying nutrition in industry: Diet and resistance to toxic substances. *J. Am. Dietet. A.* 24:473, 1948.

152. Shils, M. E., and Goldwater, L. J. Nutritional factors affecting the toxicity of some aromatic hydrocarbons with special reference to benzene and nitrobenzene compounds. *Occup. Med.* in press.

152a. Shils, M. E., and Goldwater, L. J. Influence of dietary protein and fat on the toxicities of trinitrotoluene (TNT) and 2, 4-dinitrotoluene (DNT) for the rat. *Federation Proc.* 8:397, 1949.

153. Sievers, R. F., Lawton, A. H., Skoog, F., Neal, P. A., and von Oettingen, W. F. A Medical Study of the Effect of TNT on Workers in a Bomb and Shell Loading Plant. Washington, D. C., Pub. Health. Bull. No. 291, U. S. Pub. Health Serv., 1945.

154. Simonson, E., Enzer, N., Baer, A., and Brown, R. The influence of vitamin B (complex) surplus on the capacity for muscular and mental work. *J. Indust. Hyg. & Toxicol.* 24:83, 1942.

155. Smith, W. W. Protective action of cystine and methionine in rats exposed to methyl chloride. *Federation Proc.* 5:97, 1946.

156. Smith, M. I., Westfall, B. B., and Stohlman, E. F. Experimental trinitrotoluene poisoning with attempts at detoxification. *J. Indust. Hyg. & Toxicol.* 25:39, 1943.

157. Sobel, A. E., Yuska, H., Peters, D. D., and Kramer, B. Biochemical behavior of lead: The influence of calcium, phosphorus, and vitamin D on lead in blood and bone. *J. Biol. Chem.* 132:239, 1940.

158. Spector, H., Hamilton, T. S., and Mitchell, H. H. The effect of pantothenic acid dosage and environmental temperature and humidity upon the dermal and renal excretion of pantothenic acid. *J. Biol. Chem.* 161:145, 1945.

159. Spector, H., Mitchell, H. H., and Hamilton, T. S. The effect of environmental temperature and potassium iodide supplementation on the excretion of iodine by normal human subjects. *J. Biol. Chem.* 161:137, 1945.

160. Taylor, H. L., Henschel, A., Mickelsen, O., and Keys, A. The effect of the sodium chloride intake on the work performance of man during exposure to dry heat and experimental heat exhaustion. *Am. J. Physiol.* 140:439, 1943.

161. Tennent, D. M., and Silber, R. H. The excretion of ascorbic acid, thiamine, riboflavin and pantothenic acid in sweat. *J. Biol. Chem.* 148:359, 1943.

162. Thorn, G. W., Quinby, J. T., and Clinton, M., Jr. A comparison of metabolic effects of isocaloric meals of varying composition, with special reference to prevention of postprandial hypoglycemic symptoms. *Ann. Int. Med.* 18:913, 1943.

163. Tompsett, S. L. Influence of certain constituents of diet upon the absorption of lead from the alimentary tract. *Biochem. J.* 33:1237, 1939.

164. Tourley, M. E. A survey of the diets of west coast industrial workers. *J. Am. Dietet. A.* 19:567, 1943.

165. U. S. Department of Agriculture Diets of Families of Employed Wage Earners and Clerical Workers in Cities, 1934–1936. Washington, D. C., Circular No. 507, 1939.

166. U. S. Department of Agriculture Family Food Consumption in the U. S. Spring 1942. Washington, D. C., Miscellaneous Publication No. 550, 1944.

167. Vitamin A Subcommittee, British Accessory Food Factors Comm. Vitamin A deficiency and the requirements of human adults. *Nature*, London 156:11, 1945.

168. Voegtlin, C., Hooper, C. W., and Johnson, J. M. Trinitrotoluene Poisoning. Washington, D. C., Hyg. Lab. Bull. No. 126, 1920.

169. Wald, G., Brouha, L., and Johnson, R. E. Experimental human vitamin A deficiency and the ability to perform muscular exercises. *Am. J. Physiol.* 137:551, 1942.

170. War Food Administration Industrial Feeding in Manufacturing Establishments. Washington, D. C., 1944.

171. Wiehl, D. G. Diets of a group of aircraft workers in southern California. *Milbank Mem. Fund Quart.* 20:329, 1942.

APPENDIX

TABLE A. RECOMMENDED DAILY DIETARY ALLOWANCES[1]

Revised 1948

Food and Nutrition Board, National Research Council

	Calories[2]	*Protein* (*Gm.*)	*Calcium* (*Gm.*)	*Iron* (*mg.*)	*Vitamin A*[2] (*I.U.*)	*Thiamine*[4] (*mg.*)	*Riboflavin*[4] (*mg.*)	*Niacin*[4] (*mg.*)	*Ascorbic acid* (*mg.*)	*Vitamin D* (*I.U.*)
Man (154 lb., 70 Kg.)										
Sedentary	2400	70	1.0	12[5]	5000	1.2	1.8	12	75	[6]
Physically active	3000	70	1.0	12[5]	5000	1.5	1.8	15	75	[6]
With heavy work	4500	70	1.0	12[5]	5000	1.8	1.8	18	75	[6]
Woman (123 lb., 56 Kg.)										
Sedentary	2000	60	1.0	12	5000	1.0	1.5	10	70	[6]
Moderately active	2400	60	1.0	12	5000	1.2	1.5	12	70	[6]
Very active	3000	60	1.0	12	5000	1.5	1.5	15	70	[6]
Pregnancy (latter half)	2400[7]	85	1.5	15	6000	1.5	2.5	15	100	400
Lactation	3000	100	2.0	15	8000	1.5	3.0	15	150	400
Children up to 12 yrs.[8]										
Under 1 yr.[9]	110/2.2 lb. (1 Kg.)	3.5/2.2 lb. (1 Kg.)	1.0	6	1500	0.4	0.6	4	30	400
1-3 yrs. (27 lb., 12 Kg.)	1200	40	1.0	7	2000	0.6	0.9	6	35	400
4-6 yrs. (42 lb., 19 Kg.)	1600	50	1.0	8	2500	0.8	1.2	8	50	400
7-9 yrs. (58 lb., 26 Kg.)	2000	60	1.0	10	3500	1.0	1.5	10	60	400
10-12 yrs. (78 lb., 35 Kg.)	2500	70	1.2	12	4500	1.2	1.8	12	75	400
Children over 12 yrs.[8]										
Girls,										
13-15 yrs. (108 lb., 49 Kg.)	2600	80	1.3	15	5000	1.3	2.0	13	80	400
16-20 yrs. (122 lb., 55 Kg.)	2400	75	1.0	15	5000	1.2	1.8	12	80	400
Boys,										
13-15 yrs. (108 lb., 49 Kg.)	3200	85	1.4	15	5000	1.5	2.0	15	90	400
16-20 yrs. (141 lb., 64 Kg.)	3800	100	1.4	15	6000	1.7	2.5	17	100	400

[1] Objectives toward which to aim in planning practical dietaries: The recommended allowances can be attained with a good variety of common foods which will also provide other minerals and vitamins for which requirements are less well known.

[2] Calorie allowances must be adjusted up or down to meet specific needs. The calorie values in the table are therefore not applicable to all individuals but rather represent group averages. The proper calorie allowance is that which over an extended period will maintain body weight or rate of growth at the level most conducive to well-being.

[3] The allowance depends on the relative amounts of vitamin A and carotene. The allowances of the table are based on the premise that approximately two-thirds of the vitamin A value of the average diet in this country is contributed by carotene and that carotene has half or less than half the value of vitamin A.

[4] For adults (except pregnant and lactating women) receiving diets supplying 2000 calories or less, such as reducing diets, the allowances of thiamine and niacin may be 1 mg. and 10 mg. respectively. The fact that figures are given for different calorie levels for thiamine and niacin does not imply that we can estimate the requirement of these factors within 500 calories, but they are added merely for simplicity of calculation. In the present revision, riboflavin allowances are based on body weight rather than caloric levels. Other members of the B complex also are required, though no values can be given. Foods supplying adequate thiamine, riboflavin, and niacin will tend to supply sufficient of the remaining B vitamins.

[5] There is evidence that the male adult needs relatively little iron. The need will usually be provided for if the diet is satisfactory in other respects.

[6] The need for supplemental vitamin D by vigorous adults leading a normal life seems to be minimum. For persons working at night and for nuns and others whose habits shield them from the sunlight, as well as for elderly persons, the ingestion of small amounts of vitamin D is desirable.

[7] During the latter part of pregnancy the calorie allowance should increase to approximately 20 percent above the preceding level. The value of 2400 calories represents the allowance of pregnant, sedentary women.

[8] Allowances for children are based on the needs for the middle year in each group (as 2, 5, 8, etc.) and are for moderate activity and for average weight at the middle year of the age group.

[9] Needs for infants increase from month to month with size and activity. The amounts given are for approximately 6 to 8 months. The dietary requirements for some of the nutrients such as protein and calcium are less if derived largely from human milk.

Further recommendations:

FAT. There is available little information concerning the human requirement for fat. Fat allowances must be based at present more on food habits than on physiological requirements. While a requirement for certain unsaturated fatty acids (the linoleic and arachidonic acids of natural fats) has been amply demonstrated with experimental animals, the human needs for these fatty acids is not known. In spite of the paucity of information on this subject there are several factors which make it desirable (1) that fat be included in the diet to the extent of at least 20 to 25 percent of the total calories and (2) that the fat intake include essential unsaturated fatty acids to the extent of at least 1 percent of the total calories.

At higher levels of energy expenditure, e.g., for a very active person consuming 4500 calories and for children and for adolescent persons, it is desirable that 30 to 35 percent of the total calories be derived from fat. Since foodstuffs such as meat, milk, cheese, nuts, etc., contribute fat to the diet, it is necessary to use separated or "visible" fats such as butter, oleomargarine, lard, or shortenings to supply only one-third to one-half of the amounts indicated.

WATER. A suitable allowance of water for adults is 2.5 liters daily in most instances. An ordinary standard for diverse persons is one milliliter for each calorie of food. Most of this quantity is contained in prepared foods. At work or in hot weather, requirements may reach 5 to 13 liters daily. Water should be allowed *ad libitum*, since sensations of thirst usually serve as adequate guides to intake except for infants and sick persons.

SALT. The needs for salt and for water are closely interrelated. A liberal allowance of sodium chloride for the adult is 5 grams daily, except for some persons who sweat profusely. The average normal intake of salt is 10 to 15 grams daily, an amount which meets the salt requirements for a water intake up to 4 liters daily. When sweating is excessive, one additional gram of salt should be consumed for each liter of water in excess of 4 liters daily. With heavy work or in hot climates 20 to 30 grams daily may be consumed with meals and in drinking water. Even then, most persons do not need more salt than usually occurs in prepared foods. It has been shown that after acclimatization persons produce sweat that contains only about 0.5 gram to the liter in contrast with a content of 2 to 3 grams for sweat of the unacclimatized person. Consequently after acclimatization, need for increase of salt beyond that of ordinary food disappears.

IODINE. The requirement for iodine is small, probably about 0.002 to 0.004 mg. daily for each kilogram of body weight, or a total of 0.15 to 0.30 mg. daily for the adult. This need is met by the regular use of iodized salt; its use is especially important in *adolescence* and *pregnancy*.

PHOSPHORUS. Available evidence indicates that the phosphorus allowances should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation. In the case of other adults the phosphorus allowances should be approximately 1.5 times those for calcium. In general it is safe to assume that if the calcium and protein needs are met through common foods, the phosphorus requirement also will be covered, because the common foods richest in calcium and protein are also the best sources of phosphorus.

COPPER. The requirement for copper for adults is about 1 to 2 mg. daily. Infants and children require approximately 0.05 mg. for each kilogram of body weight. The requirement for copper is approximately one-tenth that for iron. A good diet normally will supply sufficient copper.

VITAMIN K. The requirement for vitamin K usually is satisfied by any good diet except for the infant in utero and for the first few days after birth. Supplemental vitamin K is recommended during the last month of pregnancy. When it has not been given in this manner, it is recommended for the mother preceding delivery or for the baby immediately after birth.

FOLIC ACID. Evidence for recognizing folic acid (pteroylglutamic acid, vitamin B_c, L. casei factor or vitamin M) as an essential human nutrient is presented in the text. The quantitative requirement cannot be closely estimated from evidence now available.

TABLE B. FOOD VALUE TABLES FOR CALCULATION OF DIET RECORDS

Prepared for use of the Nutrition Section, States Relations Division U. S. Public Health Service, Federal Security Agency, and Reprinted by permission of the U. S. Public Health Service.

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We also want to express our gratitude to the food processors and manufacturers who provided data for our use in developing these tables.

SOURCES OF DATA

Tables of Food Composition in Terms of Eleven Nutrients, 1945, U. S. Department of Agriculture, Miscellaneous Publications No. 572.

Proximate Composition of American Food Materials, Charlotte Chatfield and Georgian Adams, U. S. Department of Agriculture, Circular No. 549.

Vitamin Values of Food in Terms of Common Measures, U. S. Department of Agriculture, Miscellaneous Publication No. 505.

Experiment Station Research on the Vitamin Content and the Preservation of Foods, 1944, Georgian Adams and Sybil L. Smith, U. S. Department of Agriculture, Miscellaneous Publication No. 536.

Tables of Vitamin Losses in Cooking of Foods, Committee on Food Composition, National Research Council.

Food Values of Portions Commonly Used, Anna de Planter Bowes, 6th Edition, 1946.

Nutrition in Health and Disease, Cooper, Barber, Mitchell, 9th Edition, 1941, Lippincott.

The Food Values of Breakfast Cereals, 1947, Cereal Institute, Inc.

Nutrition and Diet Therapy, Fairfax T. Proudfit and Corinne Hogden Robinson, 9th Edition, 1946, The Macmillan Company.

Food Values in Shares and Weights, Clara Mae Taylor, 1942, The Macmillan Company.

Rose's Foundations of Nutrition, MacLeod & Taylor, 4th Edition, The Macmillan Company.

Commercial companies that provided information on the weights and measures of their products.

PREFACE

In the development of public health nutrition programs, study of food habits and appraisal of the dietaries of groups of people is necessary. Evaluating diets of individuals and groups, comparing food consumption with that of another individual or group, and correlating dietary findings with laboratory and physical findings is facilitated when estimates of specific nutrients consumed are available.

It is recognized that such estimates are only approximations unless derived by direct chemical analysis. In calculated diet records errors are introduced by variations in nutrient content of similar food products, by commercial handling and storage of food stuffs, by differences in methods of preparation, particularly cooking methods, and by the difficulties in obtaining from individuals exact determinations of the amounts of food consumed. Generally the effects of errors so introduced are not great enough to invalidate data based on carefully collected diet records. Calculations based on these records provide a usable estimate of nutrients consumed by individuals.

These food value tables were prepared primarily for the use of the Nutrition Section of the United States Public Health Service to simplify the task of calculating data from large numbers of diet records taken in terms of household measures. A limited number of copies, however, are being made available for the use of physicians, nutritionists, dietitians, home economists, and similar interested professional groups. The tables are not intended for the use of consumers and should not be reproduced for general public distribution.

Many foods are eaten as prepared dishes for which proportions of the various ingredients cannot be readily obtained. Diet records were surveyed to determine the prepared dishes most frequently used. Values for these items have been calculated and incorporated in the tables, using recipes from standard cookbooks with modifications based on cooking practices observed in the course of field studies. Individual recipes were not obtained because of the tedious work entailed and because the little additional information they give is often of questionable value.

The tables include values for raw foods and for cooked food for which usable data are available (Summer, 1946). Estimated cooked food values for meat and vegetables are based on average values of cooking losses, and may need to be modified in areas where cooking practices differ markedly from the average. Cooking losses were imputed for a few other foods for which there are less adequate data. We recognize the large error inherent in accepting an arbitrary value for cooking losses, but believe the error is less than when such losses are completely ignored. In some areas, certain fried foods have appeared on diet records so often, and in such amounts, that they have made a significant contribution to the caloric content of the diet. For this reason the fat content of fried potatoes fried eggs, and doughnuts has been computed and has been included in the tables.

The weights and measures of the foods for which nutritive values are shown were drawn from comparisons of various texts, studies made by nutritionists in the field units of the Nutrition Section, food processors and manufacturers, and from other sources. Values for standard recipes have been calculated and included in the tables.

EXPLANATION OF TABLES

The foods that are commonly found on diet records obtained by the Nutrition Section's field units are included in these tables. They are listed in alphabetical order to facilitate the calculation of the nutritive value of the foods consumed.

In some cases brand names are used; however, this does not mean an endorsement of the product. In these instances, the food values given are selected as representative of several foods similar in composition, rather than being based on an analysis of the particular branded product.

The amount of food for which values are given is expressed in household measures or by dimensions in inches since the nutritionist determines as closely as possible the actual amount eaten in terms of such measurements. Equivalents in terms of grams are also given. The amounts appearing in the tables do not necessarily represent servings, but rather convenient units of measurement which may be used in calculating diet records. In setting up values for meats, dimensions are given for meat after cooking; weights (except for prepared ready-to-eat meat products) are given for meats before cooking.

In developing these tables, foods that are very similar in composition such as certain cereals, have been grouped and an average value used. A few foods have been grouped because the exact variety can seldom be obtained from the person giving the record. For example, a single figure has been given for each of three groups of fish commonly classified according to the fat and protein content. At the present time the Nutrition Section does not deem it advisable to use a single value for certain other groups of foods, for example, for all dark green leafy vegetables. Grouping of such foods may be feasible in an area after a rather complete knowledge of local food habits has provided data on the assortments of foods people eat.

Food item	*Household measure*	*Wt.* (Gm.)	*Calo-ries*
1. ALMONDS	1 C shelled	120	768
2. APPLE BETTY*	1/2 C	---	158
3. APPLE PIE (2 crusts 9" dia.)	1 piece 3½"	100	266
4. APPLES	1 small 2¼" dia.	100	64
5. APPLESAUCE			
Canned	1/2 C	100	80
6. APPRICOT PIE*	1/4	---	514
(2 crusts 9" dia.)	1/5	---	411
	1/6	---	343
7. APRICOTS			
Canned	6 halves 3T juice	100	89
Dried	10 halves	35	102
Fresh	2 to 3 medium	100	56
8. ASPARAGUS (green and blanched)			
Canned	8 - 10 small tips	100	21
Fresh			
Cooked	1 stalk 5" long	8	2
Cooked	6 stalks 5" long	50	13
Raw	1 stalk 5" long	8	2
Raw	6 stalks 5" long	50	13
9. AVOCADOS	1/2	100	265
10. BAKED APPLE*	1 3" dia.	---	135
11. BANANAS	1 medium 6" long	100	99
12. BASS, BLACK SEA			
Cooked, medium fat fish	1 serving 3" x 3" x 3/4"	100	98
Raw, medium fat fish	1 serving 3" x 3" x 3/4"	100	98
13. BEANS			
Canned			
Baked, with tomatoes	1/2 C	100	117
Baked, without tomatoes	1/2 C	100	117
Lima, green	2/3 C	100	72
Snap, string	1/2 C	100	19
Dried			
Common or kidney	1/2 C cooked	100	117
Lima	1/2 C cooked	100	117
Fresh			
Cooked			
Lima, green	2/3 C	100	131
Snap, string	1/2 C	100	42
Raw			
Lima, green	2/3 C	100	131
Snap, string	1/2 C	100	42
14. BEEF			
Cooked - all methods		100	235
Raw - all cuts		100	235
Hamburg steak	2 cakes 2½" dia. ½" thick	100	
Loin steak	1 steak 3" x 4" x ½"	100	

Calculated from ingredients.

Proteins		Fat (Gm.)	CHO (Gm.)	Calcium (mg.)	Phosphorus (mg.)	Iron (mg.)	Vitamins				
Animal (Gm.)	Vegetable (Gm.)						A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
	22.3	64.9	23.5	305	570	5.3	0	.30	.80	5.5	Trace
Trace	2.0	3.6	29.6	(17)	(29)	(0.6)	192	(.07)	(.04)	(0.6)	4
	(2.9)	(9.6)	(42.0)	(11)	(22)	1.9	(0)	(.05)	(.04)	0.4	(0)
	0.3	0.4	14.9	6	10	0.3	90	.04	.02	0.2	5
	0.2	0.1	19.7	(4)	(6)	(0.2)	(60)	.01	.01	Trace	1
	5.4	21.5	74.6	22	60	(1.6)	1,890	(.22)	(.14)	(1.9)	6
	4.4	17.2	59.7	18	48	(1.3)	1,512	(.17)	(.11)	(1.5)	4
	3.6	14.4	49.8	15	40	(1.1)	1,260	(.14)	(.09)	(1.3)	4
	0.6	0.1	21.4	(10)	(15)	(0.3)	1,350	.02	.02	0.3	4
	1.8	0.1	23.4	30	42	1.7	2,600	Trace	.06	1.2	4
	1.0	0.1	12.9	16	23	0.5	2,790	.03	.04	0.7	4
	1.6	0.3	3.0	20	34	1.0	[1]600	.06	.09	0.8	15
	0.2	Trace	0.3	2	5	0.1	80	.01	.01	0.1	2
	1.1	0.1	2.0	10	31	0.4	500	.06	.06	0.5	8
	0.2	Trace	0.3	2	5	0.1	80	.01	.01	0.1	3
	1.1	0.1	2.0	10	31	0.4	500	.08	.08	0.6	16
	1.7	26.4	5.1	10	38	0.6	290	.12	.15	1.1	16
	0.4	0.5	32.4	8	13	0.4	117	.01	.01	Trace	1
	1.2	0.2	23.0	8	28	0.6	430	.09	.06	0.6	10
19.0		2.5	0	21	218	1.0	---	.05	.07	4.2	(2)
19.0		2.5	0	21	218	1.0	---	.07	.07	4.2	(2)
	5.7	2.0	19.0	(49)	(154)	(3.4)	[2]70	.05	.05	0.8	[2]4
	5.7	2.0	19.0	(49)	(154)	(3.4)	(0)	.05	.05	0.8	(0)
	3.8	0.3	13.5	27	73	1.7	130	.03	.05	0.5	8
	1.0	0	3.8	27	19	1.4	410	.03	.05	0.3	4
	5.7	2.0	19.0	(49)	(154)	(3.4)	(0)	.05	.05	0.8	(0)
	5.7	2.0	19.0	(49)	(154)	(3.4)	(0)	.05	.05	0.8	(0)
	7.5	0.8	23.5	63	158	2.3	280	.18	.11	0.7	16
	2.4	0.2	7.7	65	44	1.1	630	.06	.08	0.5	10
	7.5	0.8	23.5	63	158	2.3	280	.25	.14	0.9	32
	2.4	0.2	7.7	65	44	1.1	630	.08	.10	0.6	19
18.2		18.0	0	11	196	2.7	(0)	.06	.13	4.4	0
18.2		18.0	0	11	196	2.7	(0)	.11	.14	4.9	0

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
14. BEEF *(Continued)*			
Rib roast or steak	2 slices 4" x 3" x ¼"	100	
Round steak	1 slice 2½" x 2-3/8" x 3/4"	100	
Stew meat 73% lean	3 pieces 1¼" x 1¼" x 1	100	
. . . . .	. . . . .		
Corned beef, canned	1 slice 3" x 2" x ¼"	25	58
Corned beef, cooked	2 slices 7" x 2" x ¼"	120	346
Dried or chipped beef	1 slice 4" x 5"	15	29
Dried or chipped beef creamed*	½ C	---	182
Hash, beef*	½ C	---	303
Meat balls*	1 ball 1½" dia.	---	158
Meat loaf*	1 slice 4" x 2½" x ½"	---	158
Meat pot-pie*	1 serving	---	264
Stew with vegetables*	1 C	---	203
15. BEET GREENS			
Cooked	½ C	100	33
Raw		100	33
16. BEETS			
Canned	2/3 C	100	39
Fresh			
Cooked	½ C	80	37
Raw		80	37
17. BISCUITS			
Baking Powder*	1	---	112
Sour Milk*	1	---	105
18. BLACKBERRIES	3/4 C	100	65
19. BLACKBERRY PIE* (2 crusts 9" dia.)	¼	---	494
	1/5	---	395
	1/6	---	329
20. BLUEBERRIES	2/3 C	100	68
21. BLUEBERRY PIE* (2 crusts 9" dia.)	¼	---	503
	1/5	---	403
	1/6	---	336
22. BLUE FISH			
Cooked, medium fat fish	1 serving 3" x 3" x 3/4"	100	98
Raw, medium fat fish	1 serving 3" x 3" x 3/4"	100	98
23. BOLOGNA	1 slice 4½" dia. 1/8" thick	30	65
	2 slices 2-1/8" dia. ¼" thick	40	87
24. BOUILLON CUBES	1 cube	5	13
25. BRAINS, BEEF	2 pieces 2½" x 1½" x 1"	100	127

Calculated from ingredients.

Proteins							*Vitamins*				
Animal (Gm.)	*Vegetable* (Gm.)	*Fat* (Gm.)	*CHO* (Gm.)	*Calcium* (mg.)	*Phosphorus* (mg.)	*Iron* (mg.)	*A* I.U.	*Thiamin* (mg.)	*Riboflavin* (mg.)	*Niacin* (mg.)	*Ascorbic* (mg.)
6.1		0	0	10	30	1.0	0	0	.05	0.7	0
19.0		0	0	10	200	2.9	0	.02	.08	1.0	0
5.1		0.9	0	3	56	0.8	(0)	.02	.03	0.6	0
9.7	0.6	12.0	8.1	103	157	1.3	439	.09	.19	1.1	1
10.7	1.5	22.1	13.7	17	159	2.2	129	.09	.11	3.6	6
7.2	0.8	10.9	6.9	59	115	1.2	131	.08	.14	1.6	2
7.2	0.8	10.9	6.9	59	115	1.2	131	.08	.14	1.6	2
6.9	4.3	9.5	33.3	53	151	2.2	1,399	(.18)	(.17)	3.0	7
8.2	2.6	8.3	21.2	33	149	2.1	1,822	.10	.11	2.9	9
	2.0	0.3	5.6	3	45	3.2	6,700	.04	.14	0.2	17
	2.0	0.3	5.6	3	45	3.2	6,700	.05	.17	0.3	31
	1.0	0	8.7	15	29	0.6	20	.01	.03	0.1	5
	1.3	0.1	7.7	22	34	0.8	16	.01	.03	0.2	4
	1.3	0.1	7.7	22	34	0.8	16	.02	.04	0.3	8
0.7	2.3	3.3	17.4	28	39	(0.6)	33	(.10)	(.09)	(0.8)	Trace
0.7	2.3	2.5	17.5	(28)	39	(0.6)	Trace	(.10)	(.09)	(0.8)	Trace
	1.2	0.8	13.2	36	34	0.9	320	.03	(.07)	(0.3)	23
	5.6	22.0	68.1	38	68	(2.0)	266	(.21)	(.17)	(1.8)	19
	4.5	17.6	54.5	30	54	(1.6)	213	(.17)	(.13)	(1.4)	15
	3.7	14.7	45.4	25	45	(1.3)	178	(.14)	(.11)	(1.2)	13
	0.6	0.6	15.1	16	13	0.8	280	(.03)	(.07)	(0.3)	16
	5.2	21.9	71.3	23	52	2.0	262	(.22)	(.18)	(1.8)	15
	4.1	17.5	57.0	18	41	1.6	210	(.17)	(.14)	(1.4)	12
	3.4	14.6	47.5	15	34	1.3	175	(.14)	(.12)	(1.2)	10
19.0		2.5	0	21	218	1.0	---	.05	.07	4.2	(2)
19.0		2.5	0	21	218	1.0	---	.07	.07	4.2	(2)
4.4		4.8	1.1	3	48	0.7	(0)	.09	.09	0.9	0
5.9		6.4	1.4	4	64	0.9	(0)	.12	.12	1.2	0
0.9		0	2.4	2	26	0.5	(0)	Trace	.04	[4]Trace	(0)
10.5		0	0	Trace	Trace	2,3	0	.20	.13	3.3	9

Food item	*Household measure*	*Wt. (Gm.)*	*Calories*
26. BRAN FLAKES (Prepared whole grain wheat cereal)			
All bran, 100%	½ C	30	96
Bran flakes, 40%	1 C	30	102
27. BREAD			
Rye, light	1 slice 3/8" thick	20	53
White, enriched	1 slice 3/8" thick	20	52
White, enriched dry crumbs	1 T	5	13
White, enriched dry crumbs	1 C	80	209
White, enriched, toasted	1 slice 3/8" thick	17	53
Whole wheat	1 slice 3/8" thick	20	52
Whole wheat, toasted	1 slice 3/8" thick	17	52
28. BREAD PUDDING*	½ C	---	200
29. BREAKFAST WHEAT (Whole grain cereal)	2/3 C cooked (dry wt.)	30	110
30. BROCCOLI			
Fresh			
Cooked	½ C	100	37
Raw		100	37
31. BROWN BETTY*	½ C	---	158
32. BROWNIES	1 average	10	44
33. BROWN SUGAR	1 T	11	42
	1 C	180	688
34. BRUSSELS SPROUTS			
Fresh			
Cooked	6 sprouts	70	41
Raw	6 sprouts	70	41
35. BUTTER	1 t	5	37
	1 T	14	103
	½ C	113	828
	1 pat	7	51
36. BUTTERMILK (cultured and churned)	1 C	245	86
37. CABBAGE			
Fresh			
Cooked	2/3 C	100	29
Raw	5/8 C shredded	50	14
38. CAKES			
Chocolate*	1 serving 3" x 2" x 1"	---	223
Fruit*	1 serving 2" x 2" x ¼"	---	96
Plain, light batter*	1 piece 2½" cube	100	327
	1 piece 3" x 2" x 1" or 1 cup cake	40	131
With boiled icing*	1 - 2-1/3" wedge or 1 piece 3" x 2" x 1" or 1 cup cake	---	253
	1 - 1" wedge	---	108

**Calculated from ingredients.*

Proteins							Vitamins				
Animal (Gm.)	Vegetable (Gm.)	Fat (Gm.)	CHO (Gm.)	Calcium (mg.)	Phosphorus (mg.)	Iron (mg.)	A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
	3.6	1.1	18.0	27	372	3.0	(0)	.10	.08	5.5	0
	2.9	0.6	21.0	17	170	1.4	(0)	.12	.05	2.3	0
	(1.3)	(0.7)	(10.0)	(4)	(19)	(0.2)	(0)	(.03)	(.01)	(0.2)	0
	1.7	0.4	10.0	(11)	(20)	(0.4)	(0)	(.05)	(.03)	(0.4)	0
	0.4	0.1	3.0	(3)	(5)	(0.1)	(0)	(.01)	(.01)	(0.1)	0
	6.8	1.6	42.0	(45)	(80)	(1.4)	(0)	(.19)	(.12)	(1.8)	0
	1.7	0.4	10.5	(11)	(20)	(0.4)	(0)	(.04)	(.03)	(0.4)	0
	1.9	0.7	9.0	(12)	74	0.5	(0)	.06	.03	0.7	0
	1.9	0.7	9.0	(12)	72	0.5	(0)	.04	.03	0.7	0
5.8	1.7	7.9	24.7	162	158	0.8	382	.11	.28	(0.6)	1
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	3.3	0.2	5.5	130	76	1.3	3,500	.06	.17	0.7	59
	3.3	0.2	5.5	130	76	1.3	3,500	.09	.21	0.9	118
Trace	2.0	3.6	29.6	(17)	(29)	(0.6)	192	(.07)	(.04)	(0.6)	4
	0.6	1.3	7.5	(2)	(6)	(0.1)	(0)	Trace	Trace	Trace	0
	(0)	(0)	(10.5)	[5]8	54	0.3	(0)	(0)	(0)	(0)	(0)
	(0)	(0)	(171.9)	[5]137	[5]67	4.7	(0)	(0)	(0)	(0)	(0)
	3.1	0.4	6.2	24	55	0.9	280	.06	(.03)	(0.2)	33
	3.1	0.4	6.2	24	55	0.9	280	.08	(.04)	(0.2)	66
Trace		4.0	Trace	1	1	0.01	[6]165	Trace	Trace	Trace	0
0.1		11.3	0.1	2	2	0.03	[6]462	Trace	Trace	Trace	0
0.7		92.0	0.5	18	18	0.20	[6]3,729	Trace	.01	0.1	0
Trace		5.7	Trace	1	1	0.01	[6]231	Trace	Trace	Trace	0
8.6		0.2	12.5	(289)	(228)	(.17)	Trace	(.10)	(.44)	(0.2)	(2)
	1.4	0.2	5.3	46	31	0.5	80	.05	.05	0.2	26
	0.7	0.1	2.6	23	16	0.2	40	.04	.03	0.2	26
1.0	2.6	7.7	34.7	25	60	(0.9)	223	(.11)	(.11)	(0.8)	Trace
1.7		3.2	15.0	28	43	1.3	46	---	---	---	---
	6.4	8.2	57.0	62	(126)	2.0	---	.03	.10	0.7	0
	2.6	3.3	23.0	25	(50)	0.8	---	.12	.04	0.3	0
0.8	2.6	4.9	49.2	33	(80)	1.3	160	.14	.07	0.3	0
0.4	1.1	2.1	20.9	14	(34)	0.5	69	.02	.03	0.1	0

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
38. CAKES *(Continued)*			
With fudge icing*	1 - 2-1/3" wedge or 1 piece 3" x 2" x 1" or 1 cup cake	---	329
	1 - 1" wedge	---	141
39. CANTALOUPE	1/4 - 5" dia.	100	23
40. CARROTS			
Canned	1/2 C	100	30
Fresh			
Cooked	2/3 C cubed	100	45
Raw	2/3 C cubed	100	45
Raw	1 medium 4" long or 1/2 C grated	50	22
41. CATFISH			
Cooked, medium fat fish	1 large serving	100	98
Raw, medium fat fish	1 large serving	100	98
42. CATSUP, TOMATO	1 T	15	16
43. CAULIFLOWER			
Fresh			
Cooked	3 flowerets 2" dia.	75	23
Cooked	1/2 C	60	19
Raw	3 flowerets 2" dia.	75	23
44. CELERY			
Fresh			
Cooked	1/2 C of 1/4" pieces	60	13
Raw	1 heart or 4 pieces 7" long	60	13
Raw	1/2 C of 1/4" pieces	60	13
45. CHARD			
Fresh			
Cooked	1/2 C	100	25
Raw		100	25
46. CHEERIOS (Prepared enriched oat cereal)	1 C	30	110
47. CHEESE			
Cheddar type	1 slice 3¼" x 3¼" x 1/8"	23	90
Cheddar type, grated	1 T	7	28
Cottage	1/2 C	120	121
Cottage	1 T	15	15
Cream	1 pkg. (3 oz.)	85	312
Cream	1 T	14	51
All other	1 oz. (1" cube)	28	110
48. CHEF'S WHITE WHEAT CEREAL (Unenriched)	2/3 C cooked (dry wt.)	30	108
49. CHERRIES			
Canned (pitted)	1/2 C	100	86
Fresh (flesh)	1/2 C	100	68
(with pits)	20-- 25 small or 15 large	100	64
50. CHERRY PIE* (2 crusts 9" dia.)	1/4	---	554
	1/5	---	443
	1/6	---	369

Calculated from ingredients.

Proteins		Fat (Gm.)	CHO (Gm.)	Calcium (mg.)	Phosphorus (mg.)	Iron (mg.)	Vitamins				
Animal (Gm.)	Vegetable (Gm.)						A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
0.5	2.9	8.4	60.2	43	(81)	1.1	99	.13	.07	0.4	Trace
0.2	1.2	3.6	25.7	19	(34)	0.4	42	.01	.04	0.1	Trace
	0.6	0.2	4.6	17	16	0.4	[7]3,420	.06	.04	0.8	33
	0.5	0.4	6.1	22	24	0.6	12,000	.03	.02	0.3	2
	1.2	0.3	9.3	29	37	0.8	12,000	.05	.05	0.4	3
	1.2	0.3	9.3	39	37	0.8	12,000	.07	.06	0.5	6
	0.6	0.2	4.6	20	18	0.4	6,000	.04	.03	0.2	3
19.0		2.5	0	21	218	1.0	---	.05	.07	4.2	(2)
19.0		2.5	0	21	218	1.0	---	.07	.07	4.2	(2)
	0.3	0.1	3.7	2	3	0.1	(282)	.01	.01	0.3	2
	1.8	0.2	3.7	16	54	0.8	68	.06	.06	0.3	26
	1.4	0.1	2.9	13	43	0.7	54	.04	.05	0.3	20
	1.8	0.2	3.7	16	54	0.8	68	.08	.08	0.4	52
	0.8	0.1	2.2	30	24	0.3	0	.01	.02	0.2	2
	0.8	0.1	2.2	30	24	0.3	0	.02	.02	0.2	4
	0.8	0.1	2.2	30	24	0.3	0	.02	.02	0.2	4
	1.4	0.2	4.4	3	36	4.0	2,800	.04	.10	0.2	19
	1.4	0.2	4.4	8	36	4.0	2,800	.06	.13	0.2	38
	4.5	2.0	19.0	45	100	1.2	(0)	.22	.04	0.5	0
5.5		7.4	0.4	201	140	(.13)	400	.01	.12	(0.1)	(0)
1.7		2.3	0.1	61	43	(.04)	122	Trace	.04	(Trace)	(0)
23.0		1.0	5.2	98	316	(.55)	(36)	.02	.35	(0.1)	(0)
2.9		0.1	0.6	12	39	(.07)	(4)	Trace	.04	(Trace)	(0)
6.0		31.4	1.4	(253)	(177)	(.14)	1,878	(.01)	.12	0.1	(0)
1.0		5.2	0.2	(42)	(29)	(.02)	309	(Trace)	.02	Trace	(0)
(6.7)		(9.0)	(0.5)	(244)	(171)	(.16)	574	.01	.15	0.1	(0)
	3.4	0.3	22.8	6	38	0.2	(0)	.02	.02	0.3	0
1.1	0.6	0.1	20.8	(11)	(14)	(0.3)	(430)	.03	.02	0.2	3
	1.1	0.5	14.8	---	---	---	---	.05	---	---	---
	1.0	0.5	14.0	---	---	---	---	.05	---	---	---
	5.6	21.5	84.6	(22)	59	1.6	(538)	(.23)	(.14)	(1.8)	4
	4.5	17.2	67.7	(18)	47	1.3	(430)	(.18)	(.11)	(1.4)	3
	3.7	14.4	56.4	(15)	39	1.1	(358)	(.15)	(.09)	(1.2)	2

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
51. CHICKEN			
Canned (boned)	1/4 C	50	88
Roast	3 slices 3½" x 2½" x 1/4"	100	175
52. CHILE CON CARNE*[9]	1 C	---	366
53. CHOCOLATE			
Milk chocolate bar	1 5¢ bar	45	239
Milk chocolate bar with almonds	1 5¢ bar	35	201
Unsweetened	1 square	30	171
54. CHOCOLATE MALTED MILK*	1 C	---	287
55. CHOCOLATE MERINGUE PIE	1 piece 3½" (1 crust 9" dia.)	120	268
56. CHOCOLATE MILK SHAKE*	1 C	---	469
57. CHOCOLATE PUDDING*	1/2 C	---	219
58. CHOCOLATE SYRUP*	1 T	---	65
	1/4 C or 4 T	---	260
59. CHOP SUEY (with soy sauce)*	1/2 C	---	266
60. COCOA			
Dry	1 T	9	30
Cooked:			
With all milk*	1 C	---	224
With milk and water*	1 C	---	139
61. COCOANUT			
Dry, shredded	1 T	5	29
	1/3 C	30	174
62. COCOANUT CUSTARD PIE	1 piece 3½" (1 crust 9" dia.)	120	268
63. COCO-WHEATS (Enriched cereal)	2/3 C cooked (dry wt.)	30	108
64. CODFISH			
Cooked, low fat, low protein	1 piece 3-1/3" x 2½" x 3/4"	100	70
Raw, low fat, low protein	1 piece 3-1/3" x 2½" x 3/4"	100	70
65. COLE SLAW*			
With boiled dressing	1/2 C	---	39
With cream and vinegar dressing	1/2 C	---	43
66. COLLARDS			
Cooked	1/2 C	100	50
Raw		100	50
67. COOKIES, assorted	1 average	10	44
68. CORN, sweet, white or yellow			
Canned	1/2 C	100	77
Fresh			
Cooked	1/2 C	100	108
Raw		100	108

**Calculated from ingredients.*

Proteins		Fat	CHO	Calcium (mg.)	Phosphorus (mg.)	Iron (mg.)	Vitamins				
Animal (Gm.)	Vegetable (Gm.)	(Gm.)	(Gm.)				A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
10.9		4.9	0	16	(109)	(1.0)	Trace	Trace	.08	1.8	1
21.8		9.8	0	32	(218)	(1.9)	Trace	.01	.15	3.7	2
14.6	6.5	21.2	22.8	(66)	(330)	(6.0)	946	.13	.17	4.8	7
	3.2	14.5	23.8	86	89	1.1	64	.04	.22	0.1	(0)
	3.1	13.4	17.1	72	87	1.0	47	.04	.18	0.2	0
	(1.6)	15.9	(5.4)	10	103	0.8	(0)	Trace	.07	0.3	(0)
7.8	0.3	13.3	34.0	253	221	0.4	(441)	.10	.38	0.1	1
	(3.4)	(11.8)	(37.2)	24	(46)	0.6	(0)	.04	.10	0.2	(0)
10.6	0.6	21.8	57.2	355	319	0.5	(662)	.12	.55	0.2	2
3.4	(0.5)	8.6	31.5	116	122	0.3	(157)	.04	.19	0.2	1
	0.2	2.0	11.6	(0)	13	0.1	(0)	Trace	.01	Trace	(0)
	0.8	8.0	46.4	(0)	52	0.4	(0)	Trace	.04	Trace	(0)
9.8	0.9	21.4	7.8	26	127	1.9	68	.41	.12	2.4	12
	(0.8)	1.7	(2.8)	11	64	0.2	(0)	Trace	.04	0.2	(0)
8.6	(0.5)	10.7	22.6	289	271	0.3	(392)	.10	.45	0.3	2
4.2	(0.5)	5.8	16.8	142	155	0.3	(192)	.05	.22	0.2	1
	0.2	2.0	2.7	2	10	0.2	0	Trace	Trace	Trace	(0)
	1.1	11.7	16.0	13	57	1.1	0	Trace	Trace	Trace	(0)
	(3.4)	(11.8)	(37.2)	24	(46)	0.6	(0)	.04	.10	0.2	(0)
	3.4	0.3	22.8	6	38	(0.4)	(0)	(.11)	(.08)	(0.4)	0
16.5		0.4	0	18	189	0.9	---	.03	.05	2.3	2
16.5		0.4	0	18	189	0.9	---	.04	.05	2.3	2
0.6	0.6	2.0	3.9	34	32	0.3	140	.04	.06	0.2	21
0.4	0.6	3.1	2.7	33	24	0.2	(156)	.03	.04	0.1	21
	3.9	0.6	7.2	249	58	1.6	6,870	.15	(.16)	(0.6)	50
	3.9	0.6	7.2	249	58	1.6	6,870	.22	(.20)	(0.8)	100
	0.6	1.3	7.5	(2)	(6)	(0.1)	(0)	(Trace)	(Trace)	(Trace)	0
	2.0	0.5	16.1	4	51	0.5	[12]200	.02	.05	0.8	5
	3.7	1.2	20.5	9	120	0.5	[12]390	.10	.11	1.1	6
	3.7	1.2	20.5	9	120	0.5	[12]390	.15	.14	1.4	12

Food item	Household measure	Wt. (Gm.)	Calories
69. CORNBREAD* (Enriched meal)	1 serving 2½" x 2" x 1" or 1 muffin	---	156
(Unenriched meal)	1 serving 2½" x 2" x 1" or 1 muffin	---	156
70. CORN FLAKES (Prepared cereal)	1 C	30	108
71. CORN MEAL White and yellow Whole (Enriched)**	1 T raw (dry wt.)	10	36
	2/3 C cooked (dry wt.)	30	108
	1/2 C raw (dry wt.)	75	270
(Unenriched)	1 T raw (dry wt.)	10	36
	2/3 C cooked (dry wt.)	30	108
	1/2 C raw (dry wt.)	75	270
Degerminated meal, grits, and hominy grits (Enriched)**	1 T raw (dry wt.)	10	36
	2/3 C cooked (dry wt.)	30	108
	1/2 C raw (dry wt.)	75	270
(Unenriched)	1 T raw (dry wt.)	10	36
	2/3 C cooked (dry wt.)	30	108
	1/2 C raw (dry wt.)	75	270
72. CORN PONE*	1	---	305
73. CORNSTARCH	1 T (dry wt.)	10	35
74. CORNSTARCH PUDDING*	1/2 C	---	184
75. CRACKED WHEAT (Whole grain cereal)	2/3 C cooked (dry wt.)	30	110
76. CRACKER MEAL	1/2 C	50	211
77. CRACKERS Soda, assorted	1 cracker	5	21
78. CRANBERRY SAUCE Canned	1/4 C	60	125
79. CREAM 20% sweet or sour	1 T	15	31
20% sweet or sour	1/2 C	120	250
80. CREAM OF WHEAT Enriched (5 minute)	2/3 C cooked (dry wt.)	30	108
Unenriched (regular)	2/3 C cooked (dry wt.)	30	108

Calculated from ingredients.

***Figures for enrichment ingredients are based on minimum standards although somewhat more is usually present - data from Dr. E. J. Lease, South Carolina Experiment Station, Clemson, S. C.*

+For yellow corn products calculate Vitamin A value as 405 I.U. per 100 gms.

Proteins		*Fat*	*CHO*	*Cal-cium*	*Phos-phorus*	*Iron*	*Vitamins*				
Ani-mal (Gm.)	*Vege-table* (Gm.)	(Gm.)	(Gm.)	(mg.)	(mg.)	(mg.)	*A* I.U.	*Thia-min* (mg.)	*Ribo-flavin* (mg.)	*Nia-cin* (mg.)	*Ascor-bic* (mg.)
2.4	2.9	4.2	24.7	(81)	119	1.1	86	.16	(.18)	1.1	(Trace)
2.4	2.9	4.2	24.7	(58)	119	1.0	86	.14	(.14)	0.7	(Trace)
	2.4	0.2	24.1	(3)	17	(0.3)	(0)	(.05)	.02	0.5	0
	0.9	0.4	7.4	11	26	0.3	(0)$^{+}$	.04	.03	0.4	0
	2.7	1.1	22.2	33	78	0.9	(0)$^{+}$	.13	.08	1.1	0
	6.8	2.8	55.5	82	182	2.2	(0)$^{+}$	.33	.20	2.6	0
	0.9	0.4	7.4	2	26	0.2	(0)$^{+}$	.03	.01	0.2	0
	2.7	1.1	22.2	5	78	0.7	(0)$^{+}$	.09	.03	0.5	0
	6.8	2.8	55.5	14	182	1.8	(0)$^{+}$	.25	.08	1.3	0
	0.7	0.1	7.9	11	14	0.3	(0)$^{+}$	.04	.03	0.4	0
	2.2	0.3	23.7	33	42	0.9	(0)$^{+}$	.13	.08	1.1	0
	5.6	0.8	59.2	82	98	2.2	(0)$^{+}$	.33	.20	2.6	0
	0.7	0.1	7.9	1	14	0.2	(0)$^{+}$	.01	---	0.1	0
	2.2	0.3	23.7	3	42	0.5	(0)$^{+}$	.03	.01	0.3	0
	5.6	0.8	59.2	8	98	1.2	(0)$^{+}$	.08	.03	0.7	0
	6.8	6.3	55.4	14	186	2.0	(0)	.31	.09	1.3	0
	Trace	Trace	8.7	Trace	Trace	Trace	(0)	(0)	(0)	(0)	0
4.3	Trace	4.8	30.9	144	114	0.1	(196)	.05	.21	0.1	1
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	4.8	5.2	36.4	11	51	0.8	(0)	(.04)	(0)	(0.3)	0
	0.5	0.5	3.6	1	5	0.1	(0)	(Trace)	(0)	(Trace)	0
	0.1	0.2	30.8	(5)	(4)	(0.2)	(18)	---	(.02)	---	1
0.4		3.0	0.6	(15)	(12)	(0.01)	(124)	(Trace)	(Trace)	(Trace)	(Trace)
3.5		24.0	4.8	(116)	(92)	(0.07)	(996)	(.04)	(.17)	(0.1)	(1)
	3.4	0.3	22.8	6	38	(0.4)	(0)	(.11)	(.08)	(0.4)	0
	3.4	0.3	22.8	6	38	0.2	(0)	.02	.02	0.3	0

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
81. CREAM PUFF			
Custard filling	1 medium	120	268
82. CUCUMBERS			
Cooked	1 medium	100	14
Raw	½ medium peeled or 8 slices	50	7
83. CUSTARD CREAM PIE (1 crust 9" dia.)	1 piece 3½"	120	268
84. CUSTARD CUP*	1/2 C	---	147
85. DANDELION GREENS			
Cooked	1/2 C	100	52
Raw		100	52
86. DOUGHNUTS*	1 - 2½" dia.	---	148
87. EGGPLANT			
Cooked	2/3 C diced	55	15
Raw		55	15
88. EGGS			
Egg white	1	30	14
Egg yolk	1	15	53
Fried*	1 medium egg	---	112
Scrambled egg or omelet*	1 medium egg	---	118
Whole, dried	1 T	5	30
Whole, dried	1 C	80	474
Whole, E.P., fresh	1 medium egg	45	71
89. FARINA			
(Wheat cereal)			
Dark, whole grain	2/3 C cooked (dry wt.)	30	110
Light, unenriched	2/3 C cooked (dry wt.)	30	108
Quaker, enriched	2/3 C cooked (dry wt.)	30	108
90. FIG BARS	1 bar	15	54
91. FIGS			
Dried	5 medium	100	300
Fresh	4 large	100	88
91a. FISH			
Class I (Medium fat fish)			
Cooked	1 medium serving	100	98
Raw	1 medium serving	100	98
Bass, Black Sea	1 serving 3" x 3" x 3/4"	100	
Blue fish	1 serving 3" x 3" x 3/4"	100	
Catfish	1 large serving	100	
Halibut	1 serving 2-1/2" x 2-1/2" x 1"	100	
Herring	1 medium fish	100	
Pike	1 large serving	100	
Class II (Low fat, low protein)			
Cooked	1 medium serving	100	70
Raw	1 medium serving	100	70
Cod	1 piece 3-1/3" x 2½" x 3/4"	100	
Haddock	1 serving 3" x 2" x 3/4"		

Calculated from ingredients.

Proteins		Fat	CHO	Calcium	Phosphorus	Iron	Vitamins				
Animal (Gm.)	Vegetable (Gm.)	(Gm.)	(Gm.)	(mg.)	(mg.)	(mg.)	A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
	(3.4)	(11.8)	(37.2)	24	(46)	0.6	(0)	.04	.10	0.2	(0)
	0.7	0.1	2.7	10	21	0.3	130	.03	.07	0.2	4
	0.4	Trace	1.4	5	10	0.2	130	.02	.04	0.1	4
	(3.4)	(11.8)	(37.2)	24	(46)	0.6	(0)	.04	.10	0.2	(0)
6.1	(0)	6.3	16.4	134	138	0.6	388	.06	.24	0.1	1
	2.7	0.7	8.8	187	70	3.1	13,650	.13	.11	(0.6)	18
	2.7	0.7	8.8	187	70	3.1	13,650	.19	.14	(0.8)	36
0.7	1.9	6.3	20.2	14	30	(0.6)	78	.08	.07	0.6	Trace
	0.6	0.1	3.0	8	20	0.2	20	.03	.02	0.3	2
	0.6	0.1	3.0	8	20	0.2	20	.04	.03	0.4	3
3.2		.0	0.2	2	5	Trace	0	0	.08	Trace	0
2.4		4.8	0.1	22	88	1.1	482	.05	.08	---	0
5.8		9.7	0.3	25	95	1.2	678	.05	.15	Trace	0
6.3		9.8	1.0	43	109	1.2	702	.06	.18	Trace	Trace
(2.4)		(2.2)	(0.1)	9	40	0.4	223	.02	.06	Trace	0
(38.6)		(34.6)	(2.1)	150	640	7.0	3,568	.28	.98	0.2	0
5.8		5.2	0.3	24	94	1.2	513	.05	.15	Trace	0
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	3.4	0.3	22.8	6	38	0.2	(0)	.02	.02	0.3	0
	3.4	0.3	22.8	6	38	(0.4)	(0)	(.11)	(.08)	(0.4)	0
	0.6	0.7	11.4	(10)	(10)	(0.2)	(0)	(Trace)	(.01)	(0.1)	0
	4.0	1.2	68.4	---	---	---	110	.30	---	---	---
	1.4	0.4	19.6	---	---	---	---	.06	---	---	2
19.0		2.5	0	21	218	1.0	---	.05	.07	4.2	(2)
19.0		2.5	0	21	218	1.0	---	.07	.07	4.2	(2)
16.5		0.4	0	18	189	0.9	---	.03	.05	2.3	2
16.5		0.4	0	18	189	0.9	---	.04	.05	2.3	2

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
91a. FISH *(Continued)*			
Class III (High fat, high protein)			
Salmon			
Canned	1/3 C	50	84
Fresh (steamed)	1 piece 2" x 3" x 3/4"	50	84
Sardines, drained solids			
Canned	5 sardines 3" long	50	104
Tuna			
Canned	1/3 C	50	147
92. FLOUR			
Buckwheat, light	1 T	8	28
Buckwheat, light	1/2 C	65	230
Rye, light	1 T	8	29
Rye, light	1/2 C	65	233
Rye, whole-grain	1 T	8	29
Rye, whole-grain	1/2 C	65	235
Wheat, patent	1 T	8	28
Wheat, patent	1/2 C	65	231
Wheat, patent, enriched	1 T	8	28
Wheat, patent, enriched	1/2 C	65	231
Whole wheat	1 T	8	29
Whole wheat	1/2 C	65	234
93. FRANKFURTER	1 small 5½" long 3/4" dia.	60	121
94. FRANKFURTER AND ROLL* (Commercial)	1	---	212
95. FRENCH DRESSING	1 T	14	59
96. FRENCH ROLLS, enriched	1 roll	35	106
97. FRENCH TOAST*	1 slice 3" x 3" x 1/2"	---	106
98. FRUIT COCKTAIL	5/12 C (1/2 C scant)	100	78
99. GELATIN	1 T	8	27
100. GINGERBREAD*	1 serving 1" x 2" x 2"	---	108
101. GRAHAM CRACKERS	1 cracker	10	42
102. GRAPEFRUIT			
Fresh	1/2 medium E.P.	100	44
103. GRAPEFRUIT AND ORANGE JUICE			
Canned	5/12 C (1/2 C scant)	100	48
104. GRAPEFRUIT JUICE			
Canned	5/12 C (1/2 C scant)	100	41
Fresh	5/12 C (1/2 C scant)	100	44
105. GRAPEFRUIT SEGMENTS			
Canned	5/12 C (1/2 C scant)	100	81
Fresh	5/12 C (1/2 C scant	100	44
106. GRAPE JUICE	1/2 C	100	74

*Calculated from ingredients.

Proteins		Fat	CHO	Calcium	Phosphorus	Iron	Vitamins				
Animal (Gm.)	Vegetable (Gm.)	(Gm.)	(Gm.)	(mg.)	(mg.)	(mg.)	A I. U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
10.3		4.8	0	34	143	0.6	[18]40	.02	.09	3.2	0
10.3		4.8	0	34	143	0.6	[18]40	.01	.09	3.2	0
12.8		5.5	0.6	18	182	0.9	145	.03	.06	2.6	0
12.0		11.0	0	15	126	0.8	65	.02	.06	4.6	0
	0.5	0.1	6.4	1	7	0.1	(0)	[14].02	[14].01	[14]0.2	0
	4.1	0.7	51.8	7	57	0.6	(0)	[14].20	[14].05	[14]1.4	0
	0.7	0.1	6.3	1	22	0.1	(0)	.01	Trace	0.1	0
	5.8	0.6	51.0	12	181	0.8	(0)	.10	.05	0.6	0
	0.9	0.1	6.0	5	30	0.4	(0)	.04	.02	0.1	0
	7.3	1.1	48.9	40	240	3.1	(0)	.31	.14	1.1	0
	0.9	0.1	6.1	2	7	0.1	(0)	.01	Trace	0.1	0
	7.0	0.6	49.3	12	60	0.5	(0)	.05	.02	0.5	0
	0.9	0.1	6.1	2	7	(0.2)	(0)	(.04)	(.02)	(0.3)	0
	7.0	0.6	49.3	12	60	(1.9)	(0)	(.29)	(.17)	(2.3)	0
	1.0	0.2	5.8	3	31	0.3	(0)	.04	.01	0.4	0
	8.4	1.3	47.1	25	250	2.5	(0)	.36	.08	3.6	0
9.1		8.5	2.0	5	98	1.4	(0)	.11	.14	1.4	0
6.8	3.3	8.7	23.1	(26)	114	1.7	(0)	(.19)	.16	2.0	0
	0.1	5.5	2.4	(1)	(1)	Trace	0	0	0	0	0
	2.9	2.1	18.9	(20)	(35)	(0.6)	(0)	(.08)	(.05)	(0.8)	0
1.2	1.7	5.4	11.5	38	48	0.5	229	.06	.08	(0.5)	Trace
	(0.4)	(0.2)	(18.6)	(9)	(12)	(0.4)	160	.01	.01	0.4	2
6.8		0	0	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Trace	1.6	2.4	19.9	42	22	1.4	92	.08	(.06)	0.9	0
	0.8	1.0	7.4	2	20	0.2	(0)	.03	.01	0.2	0
	0.5	0.2	10.1	17	18	0.3	Trace	.04	.02	0.2	40
	0.6	0.2	11.2	(20)	(18)	0.4	(50)	.05	.02	0.2	38
	0.5	0.2	9.4	8	12	0.4	Trace	.03	.02	0.2	35
	0.5	0.2	10.1	17	18	0.3	Trace	.04	.02	0.2	40
	0.6	0.2	19.1	13	14	0.3	Trace	.03	.02	0.2	30
	0.5	0.2	10.1	17	18	0.3	Trace	.04	.02	0.2	40
	0.4	0	18.2	---	---	---	---	.03	.08	---	6

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
107. GRAPENUT FLAKES (Prepared wheat cereal) (Enriched or restored)	1 C	30	106
108. GRAPENUTS (Prepared wheat cereal) (Enriched or restored)	1/4 C	30	106
109. GRAPENUT WHEAT MEAL (Unenriched cereal	2/3 C cooked (dry wt.)	30	108
110. GRAPES	24 grapes	100	74
111. GRAVY*			
With milk	1 T	---	30
	1 C	---	477
With water	1 T	---	19
	1 C	---	308
112. GRIDDLE CAKES*	1 cake 4½" dia.	---	94
113. HADDOCK			
Cooked, low fat, low protein	1 serving 3" x 2" x 3/4"	100	70
Raw, low fat, low protein	1 serving 3" x 2" x 3/4"	100	70
114. HALIBUT			
Cooked, medium fat fish	1 serving 2½" x 2½" x 1"	100	98
Raw, medium fat fish	1 serving 2½" x 2½" x 1"	100	98
115. HAMBURGER AND BUN* (Commercial)	1	---	228
116. HEART			
Cooked	3 slices	100	126
Raw	3 slices	100	126
117. HERRING			
Cooked, medium fat fish	1 medium fish	100	98
Raw, medium fat fish	1 medium fish	100	98
118. HONEY	1 T	20	64
119. ICE CREAM (plain)	1 block 3" x 3" x 3/4"	60	126
	1/2 C	70	147
	1 Dixie cup	60	126
	1/2 pint	140	294
	1 scoop 2½ in diameter	50	105
120. JAMS, MARMALADES, JELLIES	1 T (level) or 1 t (heaping)	20	58
121. JUNKET*	1/2 C	---	55
122. KALE			
Cooked	1/2 C	100	50
Raw		100	50
123. KIX (Prepared corn cereal)	1 C	30	110
124. KOLA BEVERAGES, CARBONATED	3½ oz.	100	48
	6 oz. bottle	180	86

**Calculated from ingredients.*

Proteins		Fat	CHO	Calcium	Phosphorus	Iron	Vitamins				
Animal (Gm.)	Vegetable (Gm.)	(Gm.)	(Gm.)	(mg.)	(mg.)	(mg.)	A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
	3.2	0.2	23.0	13	93	1.6	(0)	.24	.04	1.4	0
	3.2	0.2	23.0	13	93	1.6	(0)	.24	.04	1.4	0
	3.4	0.3	22.8	6	38	0.2	(0)	.02	.02	0.3	0
	0.8	0.4	16.7	17	21	0.6	80	.05	.03	0.4	4
0.5	0.1	2.4	1.5	18	15	Trace	(24)	.01	.03	Trace	Trace
8.6	1.8	37.8	24.2	293	242	0.6	(392)	.18	.46	0.8	2
	0.1	1.8	0.8	Trace	1	Trace	(0)	(Trace)	(Trace)	(Trace)	0
	1.8	28.2	12.2	4	14	0.4	(0)	(.08)	(.04)	(0.6)	0
1.6	2.0	1.4	16.8	(47)	(57)	(0.6)	70	(.10)	(.12)	(0.7)	Trace
16.5		0.4	0	18	189	0.9	---	.03	.05	2.3	2
16.5		0.4	0	18	189	0.9	---	.04	.05	2.3	2
19.0		2.5	0	21	218	1.0	---	.05	.07	4.2	(2)
19.0		2.5	0	21	218	1.0	---	.07	.07	4.2	(2)
8.2	3.3	10.5	21.6	(27)	128	1.9	(0)	(.13)	.12	2.9	0
(16.5)		(6.3)	(0.7)	10	236	6.2	(0)	.30	.84	6.1	7
(16.5)		(6.3)	(0.7)	10	236	6.2	(0)	.54	.90	6.8	14
19.0		2.5	0	21	218	1.0	---	.05	.07	4.2	(2)
19.0		2.5	0	21	218	1.0	---	.07	.07	4.2	(2)
	0.1	0	15.9	1	3	0.2	(0)	Trace	Trace	Trace	1
2.4		7.4	12.5	79	62	0.06	324	.02	.11	0.1	Trace
2.8		8.6	14.6	92	73	0.07	378	.03	.13	0.1	Trace
2.4		7.4	12.5	79	62	0.06	324	.02	.11	0.1	Trace
5.6		17.2	29.1	185	146	0.14	756	.06	.27	0.1	Trace
2.0		6.2	10.4	66	52	0.05	270	.02	.10	Trace	Trace
	0.1	0.1	14.2	2	2	(0.1)	2	Trace	Trace	Trace	1
2.2	(0)	2.4	6.2	72	57	0.04	(98)	.02	.10	Trace	Trace
	3.9	0.6	7.2	225	62	2.2	7,540	.08	.28	(0.6)	58
	3.9	0.6	7.2	225	62	2.2	7,540	.12	.35	(0.8)	115
	2.4	0.9	23.0	---	---	1.2	(0)	.15	---	0.6	0
	0	0	12.0	0	0	0	0	0	0	0	0
	0	0	21.6	0	0	0	0	0	0	0	0

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
125. KRUMBLES (Prepared whole grain wheat cereal)	2/3 C	30	111
126. LAMB			
Cooked - all methods		100	290
Raw - all cuts		100	290
Leg roast	1 slice 3½" x 4½" x ¼"	100	
Shoulder roast	4 slices 2½" x 2" x ¼"	100	
Sirloin chops	2 medium 2" x 1½" x 3/4"	100	
. . . . .	. . . . .		
Stew with vegetables*	1 C	---	228
127. LARD, BACON FAT, SUET	1 T	14	126
128. LEMONADE*	1 C	---	92
129. LEMON JELLY*	1/2 C	---	57
130. LEMON JUICE			
Fresh	1 T	15	7
	1 C	226	99
131. LEMON MERINGUE PIE (1 crust 9" dia,)	1 piece 3½"	120	268
132. LETTUCE	1/5 head	50	9
	1 large or 2 small leaves	10	2
	5 large or 10 small leaves	50	9
133. LIME JUICE			
Fresh	1 T	15	8
	1 C	240	127
134. LIVER			
Cooked	2 slices 3" x 2½" x 3/8"	90	118
Raw	2 slices 3" x 2½" x 3/8"	90	118
135. LIVER SAUSAGE	1 slice 3" dia. 1/4" thick	30	77
136. LOGANBERRIES	3/4 C	100	65
137. LUNCHEON MEAT	1 slice 4" x 3½" x 1/8"	30	81
138. MACARONI	1/4 C 1" pieces dry or 3/4 C cooked	30	108
139. MACARONI & CHEESE*	1/2 C	---	73
140. MALTEX (Unenriched wheat cereal)	2/3 C cooked (dry wt.)	30	108
141. MALT-O-MEAL (Enriched wheat cereal)	2/3 C cooked (dry wt.)	30	108
142. MARGARINE	1 T	14	103
143. MAYONNAISE	1 T	14	101
144. MEAT STOCK	1 C	170	26

**Calculated from ingredients*

Proteins							*Vitamins*				
Animal (Gm.)	*Vegetable* (Gm.)	*Fat* (Gm.)	*CHO* (Gm.)	*Calcium* (mg.)	*Phosphorus* (mg.)	*Iron* (mg.)	*A* I.U.	*Thiamin* (mg.)	*Riboflavin* (mg.)	*Niacin* (mg.)	*Ascorbic* (mg.)
	3.1	0.4	23.6	(11)	(116)	(1.1)	(0)	.06	.04	1.3	0
15.6		25.3	0	9	168	2.3	(0)	.11	.21	4.6	0
15.6		25.3	0	9	168	2.3	(0)	.18	.23	5.2	0
7.0	2.6	11.6	21.2	32	136	2.0	1,822	.14	.15	3.0	9
0		14.0	0	0	0	0	0	(0)	(0)	(0)	0
	0.2	0.2	22.1	(4)	(4)	Trace	(0)	Trace	Trace	Trace	14
0.8	0.1	0.1	13.3	1	1	Trace	(0)	Trace	Trace	Trace	4
	0.1	0.1	1.3	(2)	(2)	(Trace)	0	Trace	Trace	Trace	7
	2.0	1.4	19.7	(32)	(23)	(0.2)	0	.09	Trace	0.2	102
	(3.4)	(11.8)	(37.2)	24	(46)	0.6	(0)	.04	.10	0.2	(0)
	0.6	0.1	1.4	11	12	0.2	270	.03	.04	0.1	4
	0.1	Trace	0.3	6	2	0.1	162	.01	.01	Trace	2
	0.6	0.1	1.4	31	10	0.6	810	.03	.04	0.1	9
	0.1	Trace	1.8	(2)	(2)	(Trace)	0	(Trace)	(Trace)	(Trace)	4
	1.9	0.2	29.5	(34)	(24)	(0.2)	0	(.10)	(Trace)	(0.2)	65
(17.8)		(3.8)	(3.2)	7	336	10.9	17,280	.17	2.14	11.6	14
(17.8)		(3.8)	(3.2)	7	336	10.9	17,280	.24	2.52	14.5	28
5.0		6.2	0.4	3	71	1.6	(1,725)	.05	3.40	1.4	(0)
	1.2	0.8	13.2	36	34	0.9	320	.03	(.07)	(0.3)	23
4.6		6.8	0.5	6	51	0.4	(0)	.09	.06	0.8	0
	3.9	0.4	22.2	7	43	0.4	(0)	.04	.02	0.6	0
2.4	0.6	4.6	4.9	89	70	0.1	213	.02	.08	0.1	Trace
	3.4	0.3	22.8	6	38	0.2	(0)	.02	.02	0.3	0
	3.4	0.3	22.8	6	38	(0.4)	(0)	(.11)	(.08)	(0.4)	0
0.1		11.3	0.1	(Trace)	(2)	(Trace)	[15](277)	(0)	(0)	(0)	0
0.2		10.9	0.4	(3)	(8)	(0.1)	(29)	(.01)	(0.1)	(0)	(0)
4.1		0	2.4	---	---	---	(0)	---	---	---	(0)

Food item	Household measure	Wt. (Gm.)	Calories
145. MILK			
Condensed, sweetened	1 T	20	65
Dry:			
Malted	1 T	9	38
Skim (spray process)	1 T	9	32
Whole	1 T	8	40
Evaporated, unsweetened	1 T	15	21
	1/2 C	130	181
	1 C	255	354
Fresh:			
Chocolate flavored	1 C	245	184
Skim	1 C	245	86
Whole	1 C	245	169
146. MINCE PIE*	1/4	---	1,027
(2 crusts 9" dia.	1/5	---	822
	1/6	---	685
147. MOLASSES, CANE	1 T	20	48
	1 C	285	684
148. MONARCH FOOD OF WHEATS			
(Whole grain cereal)	2/3 C cooked (dry wt.)	30	110
149. MOTHER'S OATS			
(Whole grain cereal)	2/3 C cooked (dry wt.)	30	119
150. MUFFETS			
(Prepared whole wheat cereal)	1 biscuit	20	74
151. MUSTARD GREENS			
Cooked	1/2 C	100	28
Raw		100	28
152. NOODLES, EGG	3/4 C cooked (dry wt.)	30	116
153. OATMEAL COOKIES*	1 cookie	---	109
154. OATS, ROLLED			
(Whole grain cereal)	2/3 C cooked (dry wt.)	30	119
155. OIL, SALAD OR COOKING	1 T	14	126
156. OKRA			
Cooked	1/2 C	50	20
Raw		50	20
157. OLIVES (Green)	6	45	65
158 OMELET, EGG*	1 medium egg	---	118
159. ONIONS (green)	1 - 5¼" long ½" dia.	10	5
	5 - 5¼" long ½" dia.	50	24
160. ONIONS (mature)			
Cooked	1/2 C	100	49
Raw	1/2 C	100	49
161. ORANGE & GRAPEFRUIT JUICE			
Canned	5/12 C (1/2 C scant)	100	48

Calculated from ingredients.

Proteins		Fat	CHO	Calcium	Phosphorus	Iron	Vitamins				
Animal (Gm.)	Vegetable (Gm.)	(Gm.)	(Gm.)	(mg.)	(mg.)	(mg.)	A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
1.6		1.7	11.0	55	46	(.04)	(86)	(.01)	(.08)	(Trace)	(Trace)
1.3		0.8	6.4	32	31	.20	27	.03	.04	---	0
3.2		0.1	4.7	117	93	.05	(4)	.03	.18	0.1	1
2.1		2.1	3.0	76	58	.05	112	.02	.12	0.1	Trace
1.0		1.2	1.5	36	29	.03	60	.01	.05	Trace	Trace
9.1		10.3	12.9	316	254	.22	520	.06	.47	0.3	1
17.8		20.1	25.2	620	497	.43	1,020	.13	.92	0.5	3
7.8		5.4	26.0	267	223	.17	220	.07	.39	0.2	0
8.6		0.2	12.5	(289)	(228)	(.17)	(Trace)	.10	(.44)	(0.2)	(2)
8.6		9.6	12.0	289	228	.17	(392)	.10	.42	0.2	2
15.0	5.6	50.4	122.8	60	248	5.0	56	(.31)	.26	5.4	2
12.0	4.4	0.3	98.2	48	198	4.0	45	(.25)	.21	4.3	2
10.0	3.7	33.6	81.8	40	165	3.4	38	(.20)	.17	3.6	2
	(0)	(0)	(12.0)	55	10	1.3	(0)	.02	.03	0.6	(0)
	(0)	(0)	(171.0)	778	145	19.1	(0)	.23	.46	8.0	(0)
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	4.3	2.2	20.5	16	110	1.6	(0)	.16	.04	0.3	0
	2.1	0.3	15.7	(8)	(77)	(0.8)	(0)	.04	.03	0.8	0
	2.3	0.3	4.0	220	38	2.9	6,460	.06	.16	0.6	51
	2.3	0.3	4.0	220	38	2.9	6,460	.09	.20	0.8	102
	4.3	1.5	21.2	7	47	0.6	(60)	(.04)	(.04)	(0.6)	0
0.4	2.3	3.0	17.8	16	43	0.5	23	.04	.03	0.7	(Trace)
	4.3	2.2	20.5	16	110	1.6	(0)	.16	.04	0.3	0
0		14.0	Trace	(Trace)	(Trace)	(Trace)	(Trace)	(Trace)	(Trace)	(0)	(0)
	0.9	0.1	3.7	41	31	0.4	370	.04	.04	0.3	8
	0.9	0.1	3.7	41	31	0.4	370	.06	.05	0.4	15
	0.7	6.1	1.8	45	7	0.9	189	Trace	---	---	---
6.3		9.8	1.0	43	109	1.2	702	.06	.18	Trace	Trace
	0.1	Trace	1.1	3	4	0.1	500	Trace	.01	Trace	4
	0.5	0.1	5.3	16	22	0.3	2,500	.02	.06	Trace	18
	1.4	0.2	10.3	32	44	0.5	50	.02	.02	0.1	4
	1.4	0.2	10.3	32	44	0.5	50	.03	.02	0.1	9
	0.6	0.2	11.2	(20)	(18)	0.4	(50)	.05	.02	0.2	38

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
162. ORANGE JUICE			
Canned	5/12 C (1/2 C scant)	100	55
Fresh	5/12 C (1/2 C scant)	100	50
163. ORANGES	1 medium E.P.	100	50
164. OYSTERS (liquid and solids)			
Cooked, high fat, high protein	5 medium or 1/2 C solids	125	62
Raw, high fat, high protein	5 medium or 1/2 C solids	125	62
165. PANCAKES*	1 cake 4½" dia.	---	94
166. PARKER HOUSE ROLLS, enriched	1 roll	30	91
167. PARSNIPS			
Cooked	1/2 C	80	66
Raw		80	66
168. PASTRY (plain)*	2 crusts 9" dia. 1/4 pie	---	340
	1/5 pie	---	272
	1/6 pie	---	227
169. PEACHES			
Canned	2 halves 1 T juice	100	75
Dried	4 medium halves	32	94
Fresh	1 large E.P.	100	51
170. PEACH PIE*	1/4	---	495
(2 crusts 9" dia.)	1/5	---	396
	1/6	---	330
171. PEANUT BUTTER	1 T	15	93
172. PEANUTS (roasted)	1½ T chopped or 15 kernels	15	90
	1 - 5¢ package	35	210
173. PEARS			
Canned	2 halves 1 T juice	100	75
Fresh	1 medium E.P.	100	70
174. PEAS			
Canned			
Green	1/2 C	100	69
Dried			
Blackeyed	1/2 C cooked	100	117
Chickpeas	1/2 C cooked	100	117
Cowpeas	1/2 C cooked	100	117
Split	1/2 C cooked	100	117
Fresh			
Green			
Cooked	1/2 C	80	81
Raw		80	81
175. PECANS	12 meats or halves	15	112
176. PEP			
(Prepared wheat cereal)			
(Enriched or restored)	1 C	30	106
177. PEPPERS, GREEN			
Cooked	1/2 large	50	14
Raw	1/2 large	50	14

Calculated from ingredients.

Proteins		*Fat*	*CHO*	*Calcium*	*Phosphorus*	*Iron*	*Vitamins*				
Animal (Gm.)	*Vegetable* (Gm.)	(Gm.)	(Gm.)	(mg.)	(mg.)	(mg.)	*A* I.U.	*Thiamin* (mg.)	*Riboflavin* (mg.)	*Niacin* (mg.)	*Ascorbic* (mg.)
	0.6	0.1	12.9	(33)	(23)	(0.4)	(100)	.07	.02	0.2	42
	0.9	0.2	11.2	33	23	0.4	190	.08	.03	0.2	49
	0.9	0.2	11.2	33	23	0.4	(190)	.08	.03	0.2	49
7.5		1.5	4.6	85	215	8.9	---	.15	.29	1.5	---
7.5		1.5	4.6	85	215	8.9	---	.22	.29	1.5	---
1.6	2.0	1.4	16.8	(47)	(57)	(0.6)	70	(.10)	(.12)	(0.7)	Trace
	2.5	1.8	16.2	(17)	(30)	(0.5)	(0)	(.07)	(.03)	(0.7)	0
	1.2	0.4	14.6	46	64	0.6	0	.06	.06	0.2	7
	1.2	0.4	14.6	46	64	0.6	0	.09	.07	0.2	14
	4.6	21.4	32.2	8	40	(1.2)	0	(.19)	(.11)	(1.5)	0
	3.7	17.1	25.8	6	32	(1.0)	0	(.15)	(.09)	(1.2)	0
	3.1	14.2	21.5	5	26	(0.8)	0	(.12)	(.07)	(1.0)	0
	0.4	0.1	18.2	(5)	(14)	(0.4)	450	.01	.02	0.7	4
	1.0	0.2	22.2	14	40	2.2	1,040	Trace	.06	1.7	6
	0.5	0.1	12.0	8	22	0.6	880	.02	.05	0.9	8
	5.2	21.5	70.2	15	59	(1.8)	630	(.20)	(.14)	(2.5)	6
	4.1	17.2	56.1	12	47	(1.4)	504	(.16)	(.11)	(2.0)	4
	3.4	14.4	46.8	10	39	(1.2)	420	(.14)	(.09)	(1.6)	4
	3.9	7.2	3.2	11	59	0.3	0	.03	.02	2.4	(0)
	4.0	6.6	3.5	11	59	0.3	0	[16].04	.02	2.4	(0)
	9.4	15.5	8.3	26	138	0.7	---	[16].10	.06	5.7	(0)
	0.2	0.1	18.4	(8)	(10)	(0.2)	Trace	.01	.02	0.1	2
	0.7	0.4	15.8	13	16	0.3	20	.02	.04	0.1	4
	3.4	0.4	12.9	25	67	1.8	540	.11	.06	0.9	8
	5.7	2.0	19.0	(49)	(154)	(3.4)	(0)	.05	.05	0.8	(0)
	5.7	2.0	19.0	(49)	(154)	(3.4)	(0)	.05	.05	0.8	(0)
	5.7	2.0	19.0	(49)	(154)	(3.4)	(0)	.05	.05	0.8	(0)
	5.7	2.0	19.0	(49)	(154)	(3.4)	(0)	.05	.05	0.8	(0)
	5.4	0.3	14.2	18	98	1.5	544	.20	.11	1.4	10
	5.4	0.3	14.2	18	98	1.5	544	.29	.14	1.7	21
	1.4	11.0	2.0	11	49	0.4	8	.11	.02	0.1	Trace
	3.1	0.5	22.0	12	98	1.2	(0)	.17	.04	1.7	0
	0.6	0.1	2.8	6	12	0.2	315	.03	.02	0.2	30
	0.6	0.1	2.8	6	12	0.2	315	.04	.02	0.2	60

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
178. PETTIJOHN'S ROLLED WHEAT (Whole grain cereal)	2/3 C cooked (dry wt.)	30	110
179. PICKLES, CUCUMBER			
Sweet	1 small	30	3
180. PIKE			
Cooked, medium fat fish	1 large serving	100	98
Raw, medium fat fish	1 large serving	100	98
181. PINEAPPLE			
Canned	1 slice 3/4" thick or 2 slices 3/8" thick	100	87
Fresh	1 slice 3/4" or 2 slices 3/8" thick or 2/3 C ½" pcs. or 1/2 C cubes	100	58
182. PINEAPPLE JUICE	5/12 C (1/2 C scant)	100	54
183. PLUMS (ITALIAN PRUNES)			
Canned	2 medium 1 - 2 T juice	100	84
Fresh	2	70	39
184. PORK			
Fresh			
Cooked - all methods		100	352
Raw - medium fat, all cuts		100	352
Boston butt	1 slice 4½" x 3½" x 1/3"	100	
Chops	1 medium 1/2" thick	100	
Ham, lean	1 slice 5" x 5" x 1/4"	100	
Loin, roasted	1 piece 3¼" x 3" x 1/3"	100	
Picnic ham	1 slice 4½" x 3½" x 1/3"	100	
Salt pork, broiled	1 piece 4" x 1-3/4" x ¼"	50	166
Salt pork, fat boiled	1 piece 1" x 2" x 1"	35	273
Salt pork, fat raw	1 piece 1" x 2" x 1"	35	273
Salt prok, fat raw	1 piece 3" x 2" x 1"	100	781
Sausage links			
Cooked - broiling & frying	3 links 3" long 1/2" dia.	60	268
Raw	3 links 3" long 1/2" dia.	60	268
Sausage patties			
Cooked - all methods	1 pat 2" dia. 1/2" thick	60	268
Raw	1 pat 2" dia. 1/2" thick	60	268
Spareribs			
Cooked - all methods	5 pieces 4" x 1"	120	415
Raw	5 pieces 4" x 1"	120	415
Smoked			
Bacon, fried crisp	1 slice thin 5" long	15	30
Bacon, medium fat, raw	1 strip 1¼" x 9" x 1/8"	15	94
Canadian bacon			
Cooked - all methods	1 slice 2¼" dia. 3/16" thick	30	115
Raw - lean	1 slice 2¼" dia. 3/16" thick	30	115
Smoked			
Ham			
Cooked - all methods	1 slice 4½" x 4" x 3/8"	100	384
Raw - lean or medium fat	1 slice 4½" x 4" x 3/8"	100	384

Protein		Fat	CHO	Calcium	Phosphorus	Iron	Vitamins				
Animal (Gm.)	Vegetable (Gm.)	(Gm.)	(Gm.)	(mg.)	(mg.)	(mg.)	A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	0.2	0.1	0.6	7	7	0.3	57	Trace	.01	Trace	2
19.0		2.5	0	21	218	1.0	---	.05	.07	4.2	(2)
19.0		2.5	0	21	218	1.0	---	.07	.07	4.2	(2)
	0.4	0.1	21.1	29	7	0.6	80	07	.02	0.2	9
	0.4	0.2	13.7	16	11	0.3	130	.08	(.02)	(0.2)	24
	0.3	0.1	13.0	15	8	0.5	80	.05	.02	0.2	9
	0.4	0.1	20.4	8	12	1.1	(230)	.03	.03	0.4	1
	0.5	0.1	9.0	12	14	0.4	245	.10	(.02)	0.4	4
14.5		32.7	0	8	156	2.2	(0)	.60	.16	3.5	0
14.5		32.7	0	8	156	2.2	(0)	.92	.18	3.9	0
2.0		17.5	0	Trace	21	0.3	(0)	(.08)	(.02)	(0.4)	0
1.4		29.8	0	1	15	0.2	(0)	(.06)	(.01)	(0.3)	0
1.4		29.8	0	1	15	0.2	(0)	(.06)	(.01)	(0.3)	0
3.9		85.0	0	2	42	0.6	(0)	(.18)	(.04)	(0.9)	0
6.5		26.9	0	4	70	1.0	(0)	.08	.08	1.3	0
6.5		26.9	0	4	70	1.0	(0)	.13	.09	1.4	0
6.5		26.9	0	4	70	1.0	(0)	.08	.08	1.3	0
6.5		26.9	0	4	70	1.0	(0)	.13	.09	1.4	0
17.5		38.4	0	10	188	2.6	(0)	.72	.20	4.2	0
17.5		38.4	0	10	188	2.6	(0)	1.10	.22	4.7	0
1.4		2.7	0	0	16	0.1	(0)	(.06)	(.01)	(0.3)	0
1.4		9.8	(0.2)	2	16	0.1	(0)	(.06)	(.02)	(0.3)	0
5.1		10.5	(0.1)	3	55	0.8	(0)	.15	.05	1.0	0
5.1		10.5	(0.1)	3	55	0.8	(0)	.23	.06	1.1	0
16.9		35.0	(0.3)	10	182	2.5	(0)	.50	.17	3.4	0
16.9		35.0	(0.3)	10	182	2.5	(0)	.78	.19	3.8	0

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
185. POTATO CHIPS	10 large pieces	15	80
186. POTATOES			
Cooked:			
Baked	1 medium	150	128
Boiled	1 small or 1/2 C cubed	100	85
French fried*	10 pieces 2¼" x 1/2" x 1/2"	---	265
Mashed*	1/2 C	---	144
Pan fried*	1/2 C	---	265
Scalloped*	1/2 C	---	171
Raw	1 small or 1/2 C cubed	100	85
	1 medium	150	128
187. POTATO SALAD*	1/2 C	---	258
188. PRUNES			
Dried	4 medium	33	99
189. PRUNE WHIP*	1/2 C	---	198
190. PUMPKIN			
Canned	1/2 C	100	38
Fresh			
Cooked	1/2 C	100	36
Raw		100	36
191. PUMPKIN PIE* (1 crust 9" dia.)	1/4	---	406
	1/5	---	325
	1/6	---	271
192. QUICK OATS (Whole grain cereal)	2/3 C cooked (dry wt.)	30	119
193. RADISHES	5 medium	50	11
194. RAISINS			
Dried	1 T	8	24
	1/3 C	45	134
	1 C	135	402
195. RALSTON, SHREDDED (Prepared whole grain wheat cereal)	1 average serving	30	111
196. RALSTON WHEAT CEREAL (Whole grain)			
Instant W.W. Cereal	2/3 C cooked (dry wt.)	30	110
Regular W.W. Cereal	2/3 C cooked (dry wt.)	30	110
197. RHUBARB			
Cooked	1/2 C	100	18
198. RHUBARB PIE* (2 crusts 9" dia.)	1/4	---	546
	1/5	---	437
	1/6	---	364
199. RICE			
Brown, unenriched	3/4 C cooked (dry wt.)	30	107
White, unenriched	3/4 C cooked (dry wt.)	30	105
200. RICE FLAKES (Prepared enriched cereal)	1 C	30	106

**Calculated from ingredients.*

Proteins		Fat	CHO	Calcium	Phosphorus	Iron	Vitamins				
Animal (Gm.)	Vegetable (Gm.)	(Gm.)	(Gm.)	(mg.)	(mg.)	(mg.)	A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
1.0		5.6	7.4	4	21	0.3	8	.03	.02	0.4	3
	3.0	0.2	28.6	16	84	1.0	30	.11	.05	1.4	13
	2.0	0.1	19.1	11	56	0.7	20	.08	.03	1.0	8
	2.0	20.1	19.1	11	56	0.7	20	.08	.03	1.0	8
0.5	2.1	5.4	21.0	26	72	0.7	238	.08	.05	1.0	9
	2.0	20.1	19.1	11	56	0.7	20	.08	.03	1.0	8
2.2	2.5	5.4	26.0	85	122	0.8	236	.11	.14	1.2	10
	2.0	0.1	19.1	11	56	0.7	20	.11	.04	1.2	17
	3.0	0.2	28.6	16	84	1.0	30	.16	.06	1.8	26
2.7	1.7	19.3	16.8	25	99	1.3	271	.09	.09	0.8	7
	0.8	0.2	23.4	18	28	1.3	624	.03	.05	0.6	1
3.7	0.4	7.3	28.9	44	148	2.4	1,091	.09	.15	0.3	1
	1.0	0.3	7.9	(20)	(36)	(0.7)	3,400	.02	.06	0.5	(0)
	1.2	0.2	7.3	21	44	0.8	(3,400)	(.04)	(.06)	(0.5)	4
	1.2	0.2	7.3	21	44	0.8	(3,400)	(.05)	(.08)	(0.6)	8
3.6	3.0	14.6	62.1	128	138	2.4	2,776	(.15)	.25	1.3	Trace
2.9	2.4	11.7	49.7	102	111	1.9	2,221	(.12)	.20	1.1	Trace
2.4	2.0	9.8	41.4	85	92	1.6	1,851	(.10)	.17	0.9	Trace
	4.3	2.2	20.5	16	110	1.6	(0)	.16	.04	0.3	0
	0.6	Trace	2.1	18	16	0.5	15	.02	.02	Trace	12
	0.2	Trace	5.7	6	10	0.3	4	.01	.01	Trace	Trace
	1.0	0.2	32.0	35	58	1.5	22	.07	.04	0.2	Trace
	3.1	0.7	96.1	105	174	4.5	68	.20	.11	0.7	Trace
	3.1	0.4	23.6	(11)	(116)	(1.1)	(0)	.06	.04	1.3	0
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	0.5	0.1	3.8	17	25	0.5	30	.01	---	0.1	4
	5.6	21.5	82.6	9	68	(1.8)	30	(.20)	(.11)	(1.6)	4
	4.4	17.2	66.1	7	54	(1.5)	24	(.16)	(.09)	(1.3)	3
	3.7	14.4	55.1	6	45	(1.2)	20	(.14)	(.07)	(1.1)	3
	2.2	0.5	23.3	12	91	1.6	(0)	.09	.02	1.4	0
	2.3	0.1	23.8	3	28	0.2	(0)	.02	.01	0.4	0
	1.8	0.4	24.0	8	45	0.6	(0)	.09	.02	1.2	0

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
201. RICE KRISPIES (Prepared enriched cereal)	1 C	30	107
202. RICE PUDDING (creamy)*	1/2 C	---	185
203. ROLLED WHEAT (Whole grain cereal)	2/3 C cooked (dry wt.)	30	110
204. RUTABAGAS			
Fresh			
Cooked	1/2 C cubed	100	41
Raw	1/2 C cubed	100	41
205. SALAD DRESSING (boiled)*	1 T	---	27
206. SALMON			
Canned	1/3 C	50	84
Fresh (steamed)	1 piece 2" x 3" x 3/4"	50	84
207. SALMON CROQUETTE*	1/2 C	---	238
208. SALMON LOAF*	1/2 C	---	158
209. SARDINES, drained solids Canned	5 sardines 3" long	50	104
210. SAUERKRAUT Canned	2/3 C	100	20
211. SCRAMBLED EGG*	1 medium egg	---	118
212. SHREDDED WHEAT (Prepared whole grain cereal)	1 biscuit	30	111
213. SHREDDIES (Prepared whole grain wheat cereal)	3/4 C	30	111
214. SHRIMP Canned	1 C	100	82
215. SOUPS			
Bean*	1 C	---	64
Potato*	1 C	---	211
Split Pea*	1 C	---	102
Tomato (clear)*	1 C	---	104
Tomato (creamed)*	1 C	---	269
Vegetable*	1 C	---	150
216. SOYBEANS (mature) Whole	1/2 C	85	298
217. SOY FLOUR, FLAKES, GRITS			
Low fat	1/3 C	30	74
Medium fat	1/3 C	30	85
Full fat	1/3 C	30	112
218. SOY SAUCE	1/2 C	100	49
219. SPAGHETTI	1/4 C 1" pieces dry or 3/4 C cooked	30	108

Calculated from ingredients.

Proteins		Fat	CHO	Calcium	Phosphorus	Iron	Vitamins				
Animal (Gm.)	Vegetable (Gm.)	(Gm.	(Gm.)	(mg.)	(mg.)	(mg.)	A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
	1.7	0.1	25.0	6	30	1.7	(0)	.12	.03	1.8	0
6.7	1.0	6.7	23.5	113	151	0.9	473	.07	.25	0.3	1
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	1.1	0.1	8.9	55	41	0.4	330	.04	.05	0.4	18
	1.1	0.1	8.9	55	41	0.4	330	.06	.06	0.5	36
0.6	Trace	1.9	1.8	15	20	0.1	108	.01	.03	Trace	Trace
10.3		4.8	0	34	143	0 6	[18]40	.02	.09	3.2	0
10.3		4.8	0	34	143	0.6	[18]40	.01	.09	3.2	0
12.8	1.4	15.0	11.4	92	212	1.2	499	(.09)	.22	3.7	1
12.9	1.2	7.6	8.3	73	207	1.3	243	.07	.19	3.6	1
12.8		5.5	0.6	18	182	0.9	145	.03	.06	2.6	0
	1.1	0.2	3.4	46	31	(0.5)	Trace	.03	.20	0.2	[18]18
6.3		9.8	1.0	43	109	1.2	702	.06	.18	Trace	Trace
	3.1	0.4	23.6	(11)	(116)	(1.1)	(0)	.06	.04	1.3	0
	3.1	0.4	23.6	(11)	(116)	(1.1)	(0)	.06	.04	1.3	0
17.8		0.8	0.8	(75)	(210)	(2.0)	60	.01	.03	1.9	0
1.3	1.6	3.2	6.1	17	58	1.1	6	.05	.03	0.4	Trace
5.7	2.1	7.7	27.6	205	210	0.8	(335)	.14	.31	1.1	10
	2.4	6.4	8.5	(20)	63	1.4	(0)	.02	.02	0.4	0
Trace	1.7	5.9	10.9	10	21	(0.6)	1,281	.08	.04	0.9	16
6.3	1.5	18.3	18.5	225	197	(0.8)	1,503	.14	.35	0.9	13
5.5	3.0	0.3	28.3	43	87	1.1	2,031	.10	.06	1.2	14
	29.7	15.4	[20](10.2)	193	498	6.8	94	.97	.26	1.8	Trace
	13.4	0.3	[20](4.3	80	187	3.9	21	.33	.10	0.9	(0)
	12.8	2.0	[20](4.1)	73	183	3.9	33	.25	.10	0.8	(0)
	10.8	6.2	[20](3.4)	58	166	3.6	42	.23	.08	0.7	(0)
	2.0	1.0	9.0	---	---	---	---	---	.02	---	---
	3.9	0.4	22.2	7	43	0.4	(0)	.04	.02	0.6	0

Food item	*Household measure*	*Wt.* (Gm.)	*Calo-*
220. SPARKIES			
(Prepared enriched or restored cereal)			
Puffed Rice	1 C	15	54
Puffed Wheat	1 C	15	54
221. SPINACH			
Canned	1/2 C	100	25
Fresh			
Cooked	1/2 C	100	25
Raw	1 C	100	25
222. SQUASH			
Summer			
Cooked	1/2 C	100	19
Raw		100	19
Winter			
Cooked	1/2 C	100	44
Raw		100	44
223. STRAWBERRIES			
Fresh	12 hulled or 1/2 C	100	41
224. SUGAR			
Brown	1 T	11	42
	1 C	180	688
Granulated	1 t	4	16
	1 T	13	52
	1 C	200	796
Powdered	1 T	11	44
225. SWEET POTATOES			
Cooked:			
Baked	1 medium 5" long 2½" dia.	160	200
Boiled	1/2 C	100	125
Candied*	3 medium slices or 1/2 medium potato	---	168
Raw	1 medium 5" long 2½" dia.	160	200
226. SWEET ROLLS, unenriched	1 small 4½" dia.	70	213
227. SYRUP (Table blends)	1 T	20	59
228. TANGERINE JUICE			
(Other mandarin type orange juice)			
Fresh	1/2 C	120	60
229. TANGERINES			
(Other mandarin type oranges)			
Fresh	1 small	50	25
230. TAPIOCA PUDDING (creamy)*	1/2 C	---	128
231. TOMATOES			
Canned	1/2 C	100	21
Fresh			
Cooked	1/2 C	100	23
Raw	1 medium 2½" dia.	150	34
	1 slice 1/4" thick	30	7

**Calculated from ingredients.*

Proteins							*Vitamins*				
Animal (Gm.)	*Vegetable* (Gm.)	*Fat* (Gm.)	*CHO* (Gm.)	*Calcium* (mg.)	*Phosphorus* (mg.)	*Iron* (mg.)	*A* I.U.	*Thiamin* (mg.)	*Riboflavin* (mg.)	*Niacin* (mg.)	*Ascorbic* (mg.)
	0.8	Trace	12.5	2	13	0.3	(0)	.08	Trace	0.8	0
	1.9	0.2	11.0	4	49	0.6	(0)	.08	.04	1.2	0
	2.3	0.4	3.0	21	33	1.6	6,790	.02	.08	0.3	14
	2.3	0.3	3.2	22	55	3.0	9,420	.08	.19	0.6	30
	2.3	0.3	3.2	22	55	3.0	9,420	.12	.24	0.7	59
	0.6	0.1	3.9	15	15	0.4	260	.03	.04	0.9	8
	0.6	0.1	3.9	15	15	0.4	260	.04	.05	1.1	17
	1.5	0.3	8.8	19	28	0.6	4,950	.04	.06	0.5	4
	1.5	0.3	8.8	19	28	0.6	4,950	.05	.08	0.6	8
	0.8	0.6	8.1	28	27	0.8	60	.03	.07	0.3	60
	(0)	(0)	(10.5)	[5]8	[5]4	0.3	(0)	(0)	(0)	(0)	(0)
	(0)	(0)	(171.9)	[5]137	[5]67	4.7	(0)	(0)	(0)	(0)	(0)
	(0)	(0)	4.0	(0)	(0)	Trace	(0)	(0)	(0)	(0)	0
	(0)	(0)	13.0	(0)	(0)	Trace	(0)	(0)	(0)	(0)	0
	(0)	(0)	199.0	(0)	(0)	0.2	(0)	(0)	(0)	(0)	0
	(0)	(0)	11.0	(0)	(0)	Trace	(0)	(0)	(0)	(0)	0
	2.9	1.1	44.6	48	78	1.1	[23]12,320	.11	.08	0.9	18
	1.8	0.7	27.9	30	49	0.7	[23]7,700	.07	.05	0.6	11
Trace	1.4	4.3	30.6	25	40	0.6	6,314	.06	.04	0.4	9
	2.9	1.1	44.6	48	78	1.1	[23]12,320	.16	.10	1.1	35
	5.5	3.8	39.2	(39)	(70)	0.4	(0)	.06	.09	0.6	0
	(0)	(0)	(15.0)	9	3	0.8	0	0	Trace	Trace	(0)
	1.0	0.4	13.1	(40)	(28)	(0.5)	(504)	.08	(.04)	(0.2)	37
	0.4	0.2	5.4	(16)	(12)	(0.2)	(210)	.04	(.02)	(0.1)	16
3.8	0.1	4.1	18.8	101	93	0.3	(216)	.04	.17	0.1	1
	1.0	0.2	3.9	(11)	(27)	(0.6)	1,050	.05	.03	0.7	16
	1.0	0.3	4.0	11	27	0.6	1,100	.04	.03	0.5	12
	1.5	0.4	6.0	16	40	0.9	1,650	.09	.06	0.9	34
	0.3	0.1	1.2	3	8	0.2	330	.02	.01	0.2	7

Food item	*Household measure*	*Wt.* (Gm.)	*Calories*
232. TOMATO JUICE			
Canned	1/2 C	100	23
233. TOMATO PUREE			
Canned	1/2 C	100	40
234. TOMATO SAUCE*	1/4 C	---	80
235. TONGUE			
Cooked	3 slices 2" x 3" x 1/4"	100	202
Raw	3 slices 2" x 3" x 1/4"	100	202
236. TRIPE	1 piece 5" x 2½"	85	80
237. TUNA	1/3 C	50	147
238. TURKEY			
Cooked	1 slice 4" x 2½" x ¼"	55	144
239. TURNIP GREENS			
Cooked	1/2 C	100	37
Raw		100	37
240. TURNIPS			
Fresh			
Cooked	1/2 C	100	35
Raw		100	35
241. VEAL			
Cooked - all methods		60	110
Raw - all cuts		60	110
Chops	1 medium	60	
Cutlet, round	1 medium	60	
Leg, roast	2 slices 3" x 3-3/8" x ¼"	60	
Stew meat 74% lean	2 pieces 2½" x 1" x 1"	60	
Stew with vegetables*	1 C	---	180
242. VEGETABLE SALAD (Combination)*	3/4 C	---	61
243. VIENNA SAUSAGE			
Canned	1 - 2" long 3/4" dia.	20	42
244. WAFFLES*	1 waffle 4½" dia.	---	94
245. WALNUTS			
Black	8 - 10 halves	15	105
English	12 meats	15	105
246. WATERMELON	1/2 C cubes or balls	100	31
	1 slice 3/4" thick 6" dia.	330	102
	E.P. 1/16 medium sized melon	325	101
247. WHEATENA			
(Whole grain cereal)	2/3 C cooked (dry wt.)	30	110
248. WHEAT FLAKES			
(Prepared enriched or restored cereal)	1 C	30	106
249. WHEAT GERM	1 T	10	39

Calculated from ingredients

Proteins		*Fat*	*CHO*	*Calcium* (mg.)	*Phosphorus* (mg.)	*Iron* (mg.)	*Vitamins*				
Animal (Gm.)	*Vegetable* (Gm.)	(Gm.)	(Gm.)				*A* I.U.	*Thiamin* (mg.)	*Riboflavin* (mg.)	*Niacin* (mg.)	*Ascorbic* (mg.)
	1.0	0.2	4.3	(7)	(15)	(0.4)	1,050	.05	.03	0.7	16
	1.8	0.5	7.2	(11)	(37)	(1.1)	1,880	.09	(.07)	1.8	28
0.1	1.0	5.8	5.8	(7)	(14)	0.3	758	.04	.02	0.5	8
16.4		15.0	0.4	30	119	6.9	(0)	.15	.23	4.0	0
16.4		15.0	0.4	30	119	6.9	(0)	.22	.27	5.0	0
16.2		---	---	---	---	---	---	.01	.13	1.4	0
12.0		11.0	0	15	126	0.8	65	.02	.06	4.6	0
11.1		11.1	0	13	176	2.1	Trace	Trace	.08	1.8	1
	2.9	0.4	5.4	259	50	2.4	9,540	.07	.45	0.6	68
	2.9	0.4	5.4	259	50	2.4	9,540	.10	.56	0.8	136
	1.1	0.2	7.1	40	34	0.5	Trace	.04	.05	0.4	14
	1.1	0.2	7.1	40	34	0.5	Trace	.06	.06	0.5	28
11.5		7.2	0	7	124	1.7	(0)	.04	.09	2.1	0
11.5		7.2	0	7	124	1.7	(0)	.10	.16	3.8	0
8.6	2.6	5.6	21.2	33	154	2.2	1,822	.12	.12	2.5	9
	0.8	4.3	4.8	14	19	Trace	1,207	.04	.04	0.2	17
3.2		3.2	0	4	(33)	0.1	(0)	.01	.03	0.6	0
1.6	2.0	1.4	16.8	(47)	(57)	(0.6)	70	(.10)	(.12)	(0.7)	Trace
	2.2	9.7	2.3	12	57	0.3	4	.07	.02	0.2	Trace
	2.2	9.7	2.3	12	57	0.3	4	.07	.02	0.2	Trace
	0.5	0.2	6.9	7	12	0.2	590	.05	.05	0.2	6
	1.6	0.7	22.8	23	40	0.7	1,947	.16	.16	0.7	20
	1.6	0.7	22.4	23	39	0.7	1,918	.16	.16	0.7	19
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	3.1	0.5	22.0	12	98	1.2	(0)	.17	.04	1.7	0
	2.5	1.0	5.0	8	110	0.8	(0)	.20	.08	0.5	(0)

Food item	*Household measure*	*Wt.* (Gm.)	*Calories* (Gm.)
250. WHEATIES (Prepared enriched or restored cereal)	1 C	30	106
251. WHEAT KRISPIES (Prepared unenriched cereal) (Milled)	1 C	30	112
252. WHEATSWORTH CEREAL (Whole grain)	2/3 C cooked (dry wt.)	30	110
253. WHEAT TOASTED (Prepared unenriched cereal) (Milled)	1 C	30	112
254. YEAST (Brewer's) Dried	1 T	10	35

FOOTNOTES

1. *Based on green products, bleached products contain only a trace.*
2. *Contributed by tomatoes.*
3. *118 mg.; may not be available because of presence of oxalic acid.*
4. *Based on vegetable extract type; meat extract type may have up to 27.0 mg. of Niacin per 100 Gm.*
5. *Based on dark brown sugar; lower values for light brown sugar.*
6. *Year-round average.*
7. *Based on deeply colored varieties.*
8. *105 mg.; may not be available because of presence of oxalic acid.*
9. *Values were not available for chili powder used in this recipe.*
10. *95 mg.; may not be available beacuse of presence of oxalic acid.*
11. *160 mg.; may not be available because of presence of oxalic acid.*
12. *Based on yellow corn; white corn contains only a trace.*
13. *Based on pared cucumber; unpared contains about 260 I.U. Vitamin A per 100 Gm.*
14. *Whole-grain buckwheat flour has approximately 0.61 mg. Thiamin; 0.16 mg. Riboflavin; and 4.2 mg. Niacin per 100 Gm.*
15. *Plain margarine is considered to have no Vitamin A value.*
16. *Based on peanuts without skins; when skins are included the Thiamin value is higher.*
17. *51 mg.; may not be available because of presence of oxalic acid.*

Proteins							Vitamins				
Animal (Gm.)	Vegetable (Gm.)	Fat (Gm.)	CHO (Gm.)	Calcium (mg.)	Iron phorus (mg.)	Iron (mg.)	A I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic (mg.)
	3.1	0.5	22.0	12	98	1.2	(0)	.17	.04	1.7	0
	3.6	0.4	23.3	10	106	1.1	(0)	.04	.04	1.3	0
	3.5	0.6	22.7	11	116	1.1	(0)	.14	.04	1.4	0
	3.6	0.4	23.3	10	106	1.1	(0)	.04	.04	1.3	0
	4.6	0.2	3.7	11	189	1.8	(0)	.97	.54	3.6	(0)

18. *Based on pink salmon. Canned red salmon may have a value several times higher.*
19. *Drained solids only.*
20. *"Available" Carbohydrate.*
21. *90 mg.; may not be available beacuse of presence of oxalic acid.*
22. *81 mg.; may not be available because of presence of oxalic acid.*
23. *If pale varieties only were used, value would be very much lower.*

* * * * *

EXPLANATORY

1. - Definition of terms:

0	*None present*
Trace	*Small values that would have rounded to zero*
---	*No reliable data available*
( )	*Imputed value, usually from some other form of the same food or similar foods.*

2. - Abbreviations for measures:

t	*Standard measuring teaspoon*
T	*Standard measuring tablespoon*
C	*Standard measuring cup*

TABLE C. FOODS AS SOURCES OF THE NUTRIENT ELEMENTS

Contributions of Average Servings of Selected Foods

1. PROTEIN

	Gm.
Cottage cheese	23.0
Meats, liver, fowl, fish	20.0
Milk, whole, skimmed, 1 cup	8.6
Egg, one	5.7
Dried beans, cooked	5.7
Cheese, cheddar	5.5
Peas, fresh	5.4
Oatmeal	4.3
Peanuts	4.0
Whole wheat cereal	3.5
Whole wheat bread (1 slice)	1.9
Enriched white bread (1 slice)	1.7

2. CALCIUM

	Gm.
Milk, whole (1 cup)	0.290
Turnip greens	0.259
Collards	0.249
Kale	0.225
Mustard greens	0.220
Cheese, cheddar	0.200
Hot biscuit 4 oz. (made with self-rising flour)	0.190
Broccoli	0.130
Cauliflower	0.130
Cheese, cottage	0.012

3. IRON

	Mg.
Liver	10.9
Oysters	8.9
Chard	4.0
Dried beans, cooked	3.4
Beet greens	3.2
Spinach	3.0
Meat, av.	2.7
Turnip tops	2.4
Kale	2.2
Oatmeal	1.6
Egg, one	1.2
Whole wheat cereal	1.1
Whole wheat bread (1 slice)	0.5
Enriched white bread	0.4

4. VITAMIN A

	I.U.
Liver	17,000
Sweet potato	12,300
Carrots	12,000
Greens, av. (beet, kale, mustard, spinach, turnip)	8,000
Squash, hubbard	5,000
Apricots	2,600
Tomato juice (4 oz.)	1,000
Green beans, snap	630
Prunes	624
Fresh peas	545
Butter and enriched margarine	460
Cheese, cheddar	400
Milk, whole (1 cup)	390

5. THIAMINE

	Mg.
Pork, lean av.	0.60
Lamb	0.21
Corn bread, enriched	0.18
Liver	0.17
Oatmeal	0.16
Collards	0.15
Whole grain cereal	0.14
Potato, baked	0.11
Milk, whole (1 cup)	0.10
Potato, boiled, french fried, mashed	0.08
Whole wheat bread (1 slice)	0.06
Beef, veal, poultry, fish, av.	0.05
Enriched white bread (1 slice)	0.05

6. RIBOFLAVIN

	Mg.
Liver	2.14
Turnip greens	0.45
Milk, whole (1 cup)	0.42
Pork	0.16
Chicken	0.15
Egg (1)	0.15
Beef	0.13
Cheese, cheddar	0.12
Peas, fresh	0.11
Snap beans	0.08
Fish	0.06
Enriched white bread (1 slice)	0.03
Whole wheat bread (1 slice)	0.03

7. NIACIN

	Mg.
Liver	11.6
Bran flakes	5.5
Beef	4.4
Poultry (av)	3.7
Pork	3.5
Fish (av)	3.2
Peanuts	2.4
Fresh peas	1.4
Whole wheat cereal	1.4
Potato	1.4
Enriched corn bread (1 muffin)	1.1
Sweet potato	0.9
Dried beans, cooked	0.8
Whole wheat bread (1 slice)	0.7
Enriched white bread (1 slice)	0.4
Milk, whole (1 cup)	0.2

8. ASCORBIC ACID

	Mg.
Turnip greens, cooked	68
Strawberries	60
Orange (1 average)	49
Grapefruit (1/2 average)	40
Cantaloupe (1/4 average)	33
Green pepper	30
Cabbage, raw	26
Berries, black, blue	20
Tomato juice	16
Potato, baked	13
Banana	10
Pineapple juice	9
Lettuce	9
Potato, boiled, fried	8
Peach	8
Apple	5

TABLE D. DIETARY PATTERNS

I. NORMAL

Moderate in Fruits and Vegetables

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3] Vegetable, other[4] Fruit, other[5]	150 100 100	1 medium 1 serving 1 serving
4. Milk, cheese ice cream	Milk, whole	600	2-1/2 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry or fish Eggs	100 100	4 oz. raw weight, E.P. 2 medium
6. Bread, flour, cereals - whole grain or enriched	Whole grain or enriched bread	240	8 slices
7. Butter, fortified margarine	Butter or enriched margarine	30	6 teaspoonfuls
Other	Sugar	40	4 tablespoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2165; Carbohydrate, 275 Gm.; Protein, 88 Gm.; Fat, 80 Gm.; Calcium, 1.05 Gm.; Iron, 15.9 mg.; Vitamin A, 11,000 I.U.; Ascorbic Acid, 94 mg.; Thiamine, 1.5 mg.; Riboflavin, 2.5 mg.; Niacin, 15 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods, and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti, or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, scallions, escarole, chicory, cabbage; and other cooked vegetables, such as beets, egg plant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

2. NORMAL

High in Fruits and Vegetables

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	200	2 servings
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3]	100	1 small
	Vegetables, other[4]	300	3 servings
	Fruit, other[5]	200	2 servings
4. Milk, cheese, ice cream	Milk, whole	480	2 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, fish or poultry	100	4 oz. raw weight, E.P.
	Eggs	100	2 medium
6. Bread, flour, cereals - whole grain or enriched	Bread, whole grain or enriched	180	6 slices
	Cereal, whole grain or enriched	20	1/2 cup
7. Butter, fortified margarine	Butter or enriched margarine	20	4 teaspoonfuls
Other	Sugar or other sweetening	60	4 level tablespoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2100; Carbohydrate, 280 Gm.; Protein, 84 Gm.; Fat, 66 Gm.; Calcium, 1.06 Gm.; Iron, 17 mg.; Vitamin A, 16,000 I.U.; Ascorbic Acid, 125 mg.; Thiamine, 1.5 mg.; Riboflavin, 2.4 mg.; Niacin, 15 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods, and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti, or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, scallions, cabbage, chicory, escarole; and other cooked vegetables, such as beets, eggplant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

3. NORMAL

For Southern U. S. Food Habits

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Selected vegetables[1]	300	1-1/2 cups
2. Citrus fruit, tomato, raw cabbage	Tomatoes	200	1 cup
3. Potatoes, other vegetables and fruits	Sweet potato[2]	300	3 medium
4. Milk, cheese, ice cream	Milk, fluid	240	1 cup
5. Meat, poultry, fish, eggs, dried peas, beans	Pork[3]	100	4 oz. raw weight, E.P.
	Dried cow peas or beans, cooked	45	1-1/2 oz. dry
6. Bread, flour, cereals - whole grain or enriched	Corn meal, enriched	90	3 oz.
	Flour, self-rising, enriched	50	1-2/3 oz.
	Flour, white, enriched	50	1-2/3 oz.
7. Butter, fortified margarine	Margarine, enriched	20	4 teaspoonfuls
Other	Peanut butter	30	2 tablespoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2200; Carbohydrate, 295 Gm.; Protein, 70 Gm; Fat, 76 Gm.; Calcium, 1.4 Gm.; Iron, 22.1 mg.; Vitamin A, 25,000 I.U.; Ascorbic Acid, 200 mg.; Thiamine, 2.5 mg.; Riboflavin, 1.8 mg.; Niacin, 17.1 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] "Selected vegetables" contains a predominance of turnip greens, mustard greens, kale, dandelion greens.

[2] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[3] Calculated on average nutritive value of all pork products.

4. NORMAL

For Italian American Food Habits

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1/2 cup
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
	Tomato	100	1/2 cup
	Tomato paste	30	1 tablespoonful
3. Potatoes, other vegetables and fruits	Vegetable, other[3]	125	3/4 cup
	Fruit, other[4]	100	1 serving
4. Milk, cheese, ice cream	Milk, whole	500	2 cups
	Cheese	30	1 ounce
5. Meat, fish, poultry, eggs, dried peas, beans	Meat, poultry, or fish	100	4 oz. raw weight, E.P.
	Egg	45	1 medium
6. Bread, flour, cereals - whole grain or enriched	Whole grain or enriched bread	180	6 slices
	Paste, enriched	30	3/4 cup
7. Butter or fortified margarine	Butter or enriched margarine	30	6 teaspoonfuls
	Oil	30	2 tablespoonfuls
Other	Sugar	40	4 tablespoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2200; Carbohydrate, 232 Gm.; Protein, 77 Gm.; Fat, 106 Gm.; Calcium, 1.2 Gm.; Iron, 16.0 mg.; Vitamin A, 19,000 I.U.; Ascorbic Acid, 191 mg.; Thiamine, 1.5 mg.; Riboflavin, 2.3 mg.; Niacin, 12.6 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one orange, or 1/2 grapefruit, or 7 oz. grapefruit or tomato juice.

[3] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables such as beets, eggplant, onions, rutabagas, cauliflower.

[4] Other fruits includes all fruits, except the citrus fruits.

5. NORMAL

For Latin-American Food Habits

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Sweet potato	160	1 medium
2. Citrus fruit, tomato, raw cabbage	Orange juice[1]	200	1 cup
3. Potatoes, other vegetables and fruits	Potatoes, cooked[2]	300	2 medium
	Fruit, other[3]	100	1 serving
4. Milk, cheese, ice cream	Milk, whole	500	2 cups
	Cottage cheese	60	4 tablespoonfuls
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry, or fish	120	5 oz. raw weight, E.P.
	Egg	50	1 medium
	Dried beans	60	1 cup, cooked
6. Bread, flour, cereals - whole grain or enriched	Bread, enriched	40	2 slices
	Cereal, oatmeal	30	2/3 cup, cooked
	Rice, brown or converted	60	1-1/2 cups, cooked
7. Butter, fortified margarine	Butter or enriched margarine	10	2 teaspoonfuls
	Salad oil	15	1 tablespoonful
Other	Sugar	33	3 tablespoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains; Calories, 2380; Carbohydrate, 334 Gm.; Protein, 86 Gm.; Fat, 79 Gm.; Calcium, 1.0 Gm.; Iron 20.7 mg.; Vitamin A, 9,700 I.U.; Ascorbic Acid, 94 mg.; Thiamine, 1.5 mg.; Riboflavin, 2.23 mg.; Niacin, 14.9 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods, and/or additional foods.

[1] In place of orange juice, substitute 2 whole oranges, or 1 grapefruit, or 14 oz. of grapefruit juice or tomato juice.

[2] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti, or macaroni.

6. A 3000 CALORY DIET

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato[3]	200	2 small
	Vegetables, other[4]	100	1 serving
	Fruits, other[5]	200	2 servings
4. Milk, cheese, ice cream	Milk, whole	960	4 cups
	Cream, 20%	100	1/2 cup
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry or fish	100	4 oz. raw weight, E.P.
	Eggs	100	2 medium
6. Bread, flour, cereals - whole grain or enriched	Whole grain or enriched bread	240	8 slices
	Crackers, whole grain or enriched[6]	60	6
	Cereal, whole grain or enriched	20	1/2 cup
7. Butter, fortified margarine	Butter or fortified margarine	60	4 level tablespoonfuls
Other	Sugar	20	4 level teaspoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 3080; Carbohydrate, 340 Gm.; Protein, 113 Gm.; Fat, 141 Gm.; Calcium, 1.6 Gm.; Iron, 19 mg.; Vitamin A, 14,000 I.U.; Ascorbic Acid, 106 mg.; Thiamine, 1.8 mg.; Riboflavin, 3.4 mg.; Niacin, 17.6 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables, such as beets, eggplant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

[6] Two slices of bread may be substituted.

7. NORMAL DIETARY PATTERN DURING PREGNANCY

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3]	150	1 medium
	Vegetables, other[4]	100	1 serving
	Fruits, other[5]	100	1 serving
4. Milk, cheese, ice cream	Fluid, whole	960	4 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry, or fish	100	4 oz. raw weight, E.P.
	Egg	50	1 medium
	Beans or peas	100	1/2 cup cooked
6. Bread, flour, cereals - whole grain or enriched	Enriched or whole grain bread	240	8 slices
	Enriched or whole grain cereal	20	1/2 cup
7. Butter, fortified margarine	Butter or enriched margarine	30	6 level teaspoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2270; Carbohydrate, 270 Gm.; Protein, 100 Gm.; Fat, 88 Gm.; Calcium, 1.5 Gm.; Iron, 17 mg.; Vitamin A, 11,000 I.U.; Ascorbic Acid, 97 mg.; Thiamine, 1.7 mg.; Riboflavin, 3.0 mg.; Niacin, 16.0 mg. Many physicians will supplement this diet with 400-800 units of Vitamin D.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables, such as beets, eggplant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

8. NORMAL DIETARY PATTERN DURING LACTATION

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	200	1 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3]	150	1 medium
	Vegetables, other[4]	100	1 serving
	Fruits, other[5]	100	1 serving
4. Milk, cheese, ice cream	Fluid, whole[6]	1440	6 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry or fish	150	6 oz. raw weight, E.P.
	Egg	50	1 medium
	Beans or peas	100	1/2 cup, cooked
6. Bread, flour, cereals - whole grain or enriched	Bread, enriched or whole grain	240	8 slices
	Cereals, enriched or whole grain	20	1/2 cup
7. Butter, fortified margarine	Butter or enriched margarine	30	6 level teaspoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2820; Carbohydrate, 310 Gm.; Protein, 130 Gm.; Fat, 120 Gm.; Calcium, 2.0 Gm.; Iron, 19 mg.; Vitamin A, 12,450 I.U.; Ascorbic Acid, 140 mg.; Thiamine, 2.00 mg.; Riboflavin, 4.0 mg., Niacin, 22 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute two whole oranges, or 1 grapefruit, or 14 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables, such as beets, eggplant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

[6] If buttermilk or skimmed milk is substituted will give 500 less calories, 56 Gm. less fat, and 2300 units less Vitamin A with other nutrients essentially unchanged.

9. NORMAL DIETARY PATTERN FOR CHILDREN BETWEEN THREE AND SIX YEARS OF AGE

Basic 7 food group	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3]	100	1 small
	Vegetables, other[4]	100	1 serving
	Fruits, other[5]	100	1 serving
4. Milk, cheese, ice cream	Fluid, whole	960	4 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry, or fish	50	2 oz. raw weight, E.P.
	Egg	50	1 medium
6. Bread, flour, cereals - whole grain or enriched	Bread - whole grain or enriched	90	3 slices
7. Butter, fortified margarine	Butter or enriched margarine	20	4 level teaspoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 1450; Carbohydrate, 150 Gm.; Protein, 67 Gm.; Fat, 68 Gm.; Calcium, 1.3 Gm.; Iron, 9 mg.; Vitamin A, 9,700 I.U.; Ascorbic Acid, 90 mg.; Thiamine, 1.08; Riboflavin, 2.5 mg.; Niacin, 8.5 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods, and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables, such as beets, eggplant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

10. NORMAL DIETARY PATTERN FOR CHILDREN BETWEEN SEVEN AND ELEVEN YEARS OF AGE

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruits, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3]	100	1 small
	Vegetables, other[4]	100	1 serving
	Fruits, other[5]	100	1 serving
4. Milk, cheese, ice cream	Fluid, whole	960	4 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry or fish	100	4 oz. raw weight, E.P.
	Egg	50	1 medium
6. Bread, flour, cereals - whole grain or enriched	Bread, whole grain or enriched	180	6 slices
7. Butter, fortified margarine	Butter, or enriched margarine	30	6 level teaspoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 1900; Carbohydrate, 195 Gm.; Protein, 86 Gm.; Fat, 87 Gm.; Calcium, 1.39 Gm.; Iron, 12.6 mg.; Vitamin A, 11,000 mg.; Ascorbic Acid, 92 mg.; Thiamine, 1.4 mg.; Riboflavin, 2.8 mg.; Niacin, 13.1 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables, such as beets, eggplant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

II. NORMAL DIETARY PATTERN FOR CHILDREN BETWEEN TWELVE AND FIFTEEN YEARS OF AGE

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3]	100	1 small
	Vegetables, other[4]	100	1 serving
	Fruits, other[5]	100	1 serving
4. Milk, cheese, ice cream	Fluid, whole	960	4 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry or fish	100	4 oz. raw weight, E.P.
	Egg	100	2 medium
6. Bread, flour, cereals - whole grain or enriched	Bread, whole grain or enriched	240	8 slices
7. Butter, fortified margarine	Butter or enriched margarine	30	6 level teaspoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2120; Carbohydrate, 226 Gm.; Protein, 96 Gm.; Fat, 87 Gm.; Calcium, 1.4 Gm.; Iron, 15 mg.; Vitamin A, 11,900 I.U.; Ascorbic Acid, 93 mg.; Thiamine, 1.6 mg.; Riboflavin, 3.1 mg.; Niacin, 14.4 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables, such as beets, eggplant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

12. NORMAL DIETARY PATTERN FOR BOYS BETWEEN SIXTEEN AND TWENTY YEARS OF AGE

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3]	200	2 small
	Vegetables, other[4]	100	1 serving
	Fruits, other[5]	100	1 serving
4. Milk, cheese, ice cream	Milk, whole	1440	6 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry, or fish	100	4 oz. raw weight, E.P.
	Egg	100	2 medium
6. Bread, flour, cereals - whole grain or enriched	Bread, whole grain or enriched	310	10 slices
	Cereal, whole grain or enriched	20	1/2 cup
7. Butter, fortified margarine	Butter or enriched margarine	80	8 level teaspoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 3100; Carbohydrate, 315 Gm.; Protein, 125 Gm.; Fat, 155 Gm.; Calcium, 2.0 Gm.; Iron, 18 mg.; Vitamin A, 14,000 I.U.; Ascorbic Acid, 105 mg.; Thiamine, 2.0 mg.; Riboflavin, 4.0 mg.; Niacin, 18.0 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables, such as beets, egg plant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

13. LIQUID DIET

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1 Leafy green or yellow vegetables			
2. Citrus fruit, tomato, raw cabbage	Orange juice Tomato juice	200 100	1 cup 1/2 cup
3. Potatoes, other vegetables, and fruits			
4. Milk, cheese, ice cream	Milk, whole	1440	6 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Eggs	200	4 medium
6. Bread, flour, cereals - whole grain or enriched	Cereal, enriched[1]	20	2 tablespoonfuls
7. Butter, fortified Margarine	Butter or enriched margarine	20	4 level teaspoonfuls
Other	Bouillon cake	5	1 cube
	Cocoa	10	4 level teaspoonfuls
	Sugar	45	3 level tablespoonfuls
	Gelatin	5	1 teaspoonful

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 1850; Carbohydrate, 160 Gm.; Protein, 88 Gm.; Fat, 97 Gm.; Calcium, 1.87 Gm.; Iron, 9.6 mg.; Vitamin A, 6,430 I.U.; Ascorbic Acid 115 mg.; Thiamine, 1.1 mg.; Riboflavin, 3.5 mg.; Niacin, 5.0 mg.

This diet is unsatisfactory in iron, thiamine and niacin and should therefore be supplemented with brewers' yeast or an appropriate supplementary iron and vitamin preparation.

[1] Farina or oatmeal, dry weight.

14. LIQUID DIET FOR TUBE FEEDING

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables			
2. Citrus fruit, tomato, raw cabbage	Orange juice, strained[1]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Applesauce[2]	60	4 tablespoonfuls
4. Milk, cheese, ice cream	Milk, whole	480	2 cups
	Cream, 20%	480	2 cups
	Milk Powder, whole	120	8 tablespoonfuls
5. Meat, poultry, fish, eggs, dried peas, beans	Liver, raw, ground or pureed	120	4 oz. raw weight, E.P.
	Eggs	200	4 medium
6. Bread, flour, cereals - whole grain or enriched			
7. Butter, fortified margarine			
Other	Glucose or sucrose	100	1/2 cup
	Brewers' yeast powder	20	5 level teaspoonfuls

Adapted from Stare, F. J., and Thorn, G. W. Protein nutrition in problems of medical interest. J.A.M.A., 127:1120, 1945.

This diet contains: Calories, 2990; Carbohydrate, 226 Gm.; Protein, 122 Gm.; Fat, 177 Gm.; Calcium, 2.3 Gm.; Iron, 25 Mg.; Vitamin A, 24,000 I.U.; Ascorbic Acid, 112 mg.; Thiamine, 3.3 mg.; Riboflavin, 8.5 mg.; Niacin, 28 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

Mix all ingredients, except orange juice, in a good mechanical mixer. Gives a total value of 1440 cc. Should be made up fresh daily and kept in a closed container in the refrigerator. Give feedings of about 100 cc. conveniently spaced throughout the day and night.

[1] Give in separate feeding and flush out tube with water.

[2] Apple powder or pectin also may be used; added to prevent diarrhea.

15. SOFT, LOW-FIBER DIET

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables, pureed[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange or grapefruit juice, strained	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato or rice, cooked	150 100	1 medium 1 serving
	Fruit, other, cooked and pureed[2]		
	Vegetables, other, cooked and pureed[3]	100	1 serving
4. Milk, cheese ice cream	Milk, whole	960	4 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Lean meat, poultry, or fish, cooked	100	4 oz. raw weight E.P.
	Eggs	100	2 medium
6. Bread, flour, cereals - whole grain or enriched	Bread, white, enriched	180	6 slices
	Cereal, refined, enriched	20	1/2 cup
7. Butter, fortified margarine	Butter or enriched margarine	20	4 level teaspoonfuls
Other	Sugar	30	2 level tablespoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2100; Carbohydrate, 250 Gm.; Protein, 96 Gm.; Fat, 85 Gm.; Calcium, 1.5 Gm.; Iron, 15.1 mg.; Vitamin A, 11,000 I.U.; Ascorbic Acid, 96 mg.; Thiamine, 1.5 mg.; Riboflavin, 3.1 mg.; Niacin, 14.4 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] Other fruits includes all fruits, except the citrus fruits.

[3] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, onions, rutabagas, cauliflower.

16. BLAND DIET

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables, cooked[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, or rice, cooked	100	1 medium
	Vegetables, others, cooked[3]	100	1 serving
	Fruits, others, cooked[4]	100	1 serving
4. Milk, cheese, ice cream	Milk, whole	960	4 cups
5. Meat, poultry, fish, eggs, dried peas and beans	Meat, poultry or fish	100	4 oz. raw weight; E.P.
	Eggs	100	2 medium
6. Bread, flour, cereals - whole grain or enriched	Bread, white, enriched	180	6 slices
	Cereal, refined,	20	1/2 cup
7. Butter, fortified margarine	Butter or enriched margarine	20	4 teaspoonfuls
Other	Sugar	15	3 level teaspoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2000; Carbohydrate, 230 Gm.; Protein, 95 Gm.; Fat, 83 Gm.; Calcium, 1.45 Gm.; Iron 14 mg.; Vitamin A, 12,000 I.U.; Ascrobic Acid, 95 mg.; Thiamine, 1.6 mg.; Riboflavin, 3.0 mg.; Niacin, 14 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] Vegetables included here are beets, peas, summer squash and tomato juice or tomato soup.

[4] Fruits included here are applesauce, pear, peach, apricot, plum and sweet cherries.

17. HIGH-PROTEIN DIET

Basic 7 food groups	*Food items*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3]	200	2 small
	Vegetables, other[4]	200	2 servings
	Fruits, other[5]	200	2 servings
4. Milk, cheese, ice cream	Skim milk, fluid[6]	960	4 cups
	Dry Skim Milk solids	90	6 tablespoonfuls
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry or fish[7]	100	4 oz. raw weight, E.P.
6. Bread, flour cereals - whole grain or enriched	Bread, whole grain or enriched white	180	6 slices
	Cereal, whole grain or enriched	20	1/2 cup
7. Butter, fortified margarine[8]			
Other	Sugar	50	3½ tablespoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2100; Carbohydrate, 350 Gm.; Protein, 120 Gm.; Fat, 26 Gm.; Calcium, 2.45 Gm.; Iron, 14 mg.; Vitamin A, 9000 I.U.; Ascorbic Acid, 119 mg.; Thiamine, 1.6mg.; Riboflavin, 4.5 mg.; Niacin, 16.3 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] Or double amount of grapefruit juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables such as beets, eggplant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

[6] The substitution of whole fluid milk will increase fat by 38 Gm. and calories by 330.

[7] Doubling meat portion will increase protein to 143 Gm. and calories to 2310.

[8] Butter or enriched margarine may be added if more fat is desired. ten grams of butter or enriched margarine adds approximately 8 grams of fat and 70 calories.

18. LOW-FAT DIET

Basic 7 food groups	*Food items*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables or fruits	Potato, cooked[3]	200	2 small
	Vegetables, other[4]	200	2 servings
	Fruits, other[5]	200	2 servings
4. Milk, cheese, ice cream	Milk, fluid, skimmed	960	4 cups
	Milk, dry, skimmed	90	10 tablespoonfuls
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, lean; poultry or fish, cooked	100	4 oz. raw weight E.P.
6. Bread, flour, cereals - whole grain or enriched	Bread, whole grain or enriched	180	6 slices
	Cereal, whole grain or enriched	20	1/2 cup
7. Butter, fortified margarine			
Other	Sugar	50	3-1/3 tablespoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2100; Carbohydrate, 350 Gm.; Protein, 120 Gm.; Fat, 26 Gm.; Calcium, 2.4 Gm.; Iron, 14 mg.; Vitamin A, 9000 I.U.; Ascorbic Acid, 119 mg.; Thiamine, 1.6 mg.; Riboflavin, 4.5 mg.; Niacin, 16.3 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The equivalent amount of potato substitute may be used, such as: rice, navy beans, other dried beans, spaghetti or macaroni.

[4] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables, such as beets, eggplant, onions, rutabagas, cauliflower.

[5] Other fruits includes all fruits, except the citrus fruits.

19. LOW-CHOLESTEROL DIET

Basic 7 food groups	*Food item*	*Weight (Gm.)*	*Approximate measure*
1. Leafy green or yellow vegetables	Vegetables[1]	100	1 serving
2. Citrus fruit, tomato, raw cabbage	Orange juice[2]	100	1/2 cup
3. Potatoes, other vegetables and fruits	Potato, cooked[3] Vegetables, other[4] Fruits, other[5]	200 100 200	2 small 1 serving 2 servings
4. Milk, cheese, ice cream	Skimmed milk	960	4 cups
5. Meat, poultry, fish, eggs, dried peas, beans	Meat, poultry or fish (no fatty meats) (trim all fat)	150	6 oz. raw weight, E.P.
6. Bread, flour, cereals - whole grain or enriched	Bread, whole grain or enriched Cereal, whole grain or enriched	180 20	6 slices 1/2 cup
7. Butter, fortified margarine	Fortified margarine	60	4 tablespoonfuls

From The Nutrition Clinic, Department of Health of the City of New York, Revised 1948.

This diet contains: Calories, 2200; Carbohydrate, 240 Gm.; Protein, 96 Gm.; Fat, 82 Gm.; Calcium, 1.3 Gm.; Iron, 14 mg.; Vitamin A., 7,900 I.U.; Ascorbic Acid, 106 mg.; Thiamine, 1.4 mg.; Riboflavin, 2.7 mg.; Niacin, 17.4 mg.

The specific nutrients in this diet are adequate in all respects. The caloric value of this diet may be increased, preferably by larger servings of these foods and/or additional foods.

[1] The leafy green and yellow vegetables to be included in this category are: asparagus, brocolli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, dandelion greens, mustard greens, beet tops.

[2] In place of orange juice, substitute one whole orange, or 1/2 grapefruit, or 7 oz. grapefruit juice or tomato juice.

[3] The other vegetables to be included in this category are: tomatoes, fresh, canned or juice; vegetables commonly served raw, such as celery, cucumber, lettuce, chicory, escarole, scallions, cabbage; and other cooked vegetables, such as beets, egg plant, onions, rutabags, cauli-

[4] The equivalent amount of potato substitute may be used, such as: rice navy beans, other dried beans, spaghetti or macaroni.

[5] Other fruits includes all fruits, except the citrus fruits.

TABLE E. IDEAL WEIGHTS FOR MEN*

Height (with shoes on) *Ft.*	*In.*	*Small frame*	*Medium frame*	*Large frame*
5	2	116-125	124-133	131-142
5	3	119-128	127-136	133-144
5	4	122-132	130-140	137-149
5	5	126-136	134-144	141-153
5	6	129-139	137-147	145-157
5	7	133-143	141-151	149-162
5	8	136-147	145-156	153-166
5	9	140-151	149-160	157-170
5	10	144-155	153-164	161-175
5	11	148-159	157-168	165-180
6	0	152-164	161-173	169-185
6	1	157-169	166-178	174-190
6	2	163-175	171-184	179-196
6	3	168-180	176-189	184-202

Weight in pounds according to frame, as ordinarily dressed.

*From Metropolitan Life Insurance Company: Ideal weights for men. Metropolitan Life Ins. Bull. 24:6, 1943.

TABLE F. IDEAL WEIGHTS FOR WOMEN*

Height (with shoes on) Ft. In.	*Small frame*	*Medium frame*	*Large frame*
4 11	104-111	110-118	117-127
5 0	105-113	112-120	119-129
5 1	107-115	114-122	121-131
5 2	110-118	117-125	124-135
5 3	113-121	120-128	127-138
5 4	116-125	124-132	131-142
5 5	119-128	127-135	133-145
5 6	123-132	130-140	138-150
5 7	126-136	134-144	142-154
5 8	129-139	137-147	145-158
5 9	133-143	141-151	149-162
5 10	136-147	145-155	152-166
5 11	139-150	148-158	155-169

Weight in pounds according to frame, as ordinarily dressed.

*From Metropolitan Life Insurance Company: Ideal weights for women. Metropolitan Life Ins. Bull. 23: 6, 1943.

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